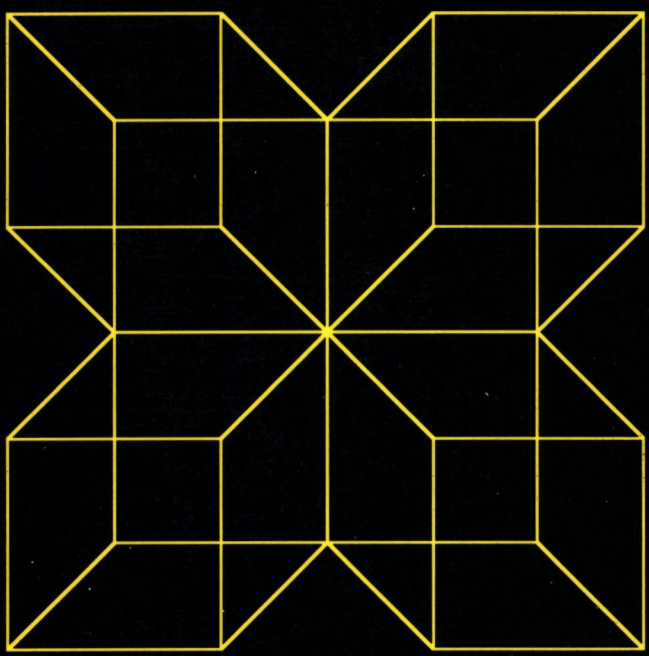
CHIRAL OXAZABOROLIDINE CATALYZED ASYMMETRIC CYCLOADDITION REACTION



Jean-Paul G. Seerden

CHIRAL OXAZABOROLIDINE CATALYZED ASYMMETRIC CYCLOADDITION REACTIONS

een wetenschappelijke proeve op het gebied van de Natuurwetenschappen

Proefschrift ter verkrijging van de graad van doctor aan de Katholieke Universiteit Nijmegen, volgens besluit van het College van Decanen in het openbaar te verdedigen op maandag 16 oktober 1995, des namiddags te 1.30 uur precies

door

Johannes Paulus Gerardus Seerden

geboren op 21 augustus 1966 te Weert

Promotor : prof dr. R.J M. Nolte

Co-promotor : dr. J.W. Scheeren

This work was supported by the Innovation Oriented Research Program on Catalysis (IOP-Katalyse, no. 90034) of the Netherlands Ministry of Economic Affairs.

Realisatie. Universitair Publikatiebureau KUN
ISBN 90-373-0297-1

"Working models can not be proven,

they can only be eliminated"

Aan mijn ouders

Dankwoord

Een proefschrift komt tot stand door de inspanning van meerdere mensen Een woord van dank is daarom op zijn plaats Allereerst wil ik mijn ouders bedanken die het mij mogelijk hebben gemaakt om te kunnen gaan studeren en voor hun steun en belangstelling tijdens het onderzoek Dr Hans Scheeren en Prof Dr Roeland Nolte wil ik bedanken voor het vertrouwen in mij en voor de prettige discussies over van-alles-en-nog-wat Beste Hans, de grote mate van vrijheid die ik genoot tijdens het onderzoek heeft een belangrijke meerwaarde aan het werk gegeven

De hoofdvakstudenten die hebben meegewerkt aan het onderzoek wil ik heel hartelijk bedanken voor hun grote inzet en toewijding De soms lastige cyclohexenonen werden allereerst in de watten gelegd door 'Mama' Elma Schenkelaars waarna 'Sp*e e* dy' Liesbeth Schoevaars ze onder hoge druk aan de praat kreeg De nitronen werden door 'Bruine Buik' Anita Scholte op Reimer aange"boor"d en zodanig verwend met ket*e e* nacetalen dat ze door 'Bedáááánkt voor de bloeoeme' Mike Boeren (MMM-*e e* n) achtervolgd werden met vinylethers Een aparte oplossing van 'de Specialist' Marcel Kuypers (MMM-tw*e e*) bracht de nitronen tenslotte tot ongekende prestaties

Een speciaal woord van dank ben ik verschuldigd aan René Aben, de drijvende kracht in de werkgroep Ondanks de soms verschillende manieren heb ik van hem veel praktische (niet-) chemische dingen geleerd De lab- en koffietafelgenoten Ruben Leenders (β-Fender), Peter Wiegerinck (v/d Tax), Gerben Gieling (MacHelp), Dirk (Kees) Vandenput (5thMan&cigar), Erik van Roozendaal (biljartkoning), Jan van Maarseveen (McMac), Dries de Bont, Ruud Schuurman, Fokke Venema, Martin Feiters, Hanny van Nunen, Nico Sommerdijk, Johnny Bouwmeesters, Lizette Fluks, Connie van Ravenswaay, Marion Pennekamp, Jeannet Hammink, Marcel van der Rijst en alle hoofd- en bijvakkers van de afgelopen jaren bedank ik voor de gezelligheid op het lab en voor het geleende glaswerk Ad Swolfs, Peter van Galen, Helene Amatdjais-Groenen, Pieter van de Meer, Chris Kroon, Wim van Luyn en Sandra Tijdink bedank ik voor hun onmisbare analytische, technische en logistieke ondersteuning Voor het denken en evalueren op IOP-niveau waren Adri van der Waals en Patricia Gosling prettige gesprekspartners Geert-Jan Willems wordt bedankt voor het gedeelde chirale HPLC-leed en -plezier

Prof Dr G I Tesser en Hans Adams worden bedankt voor hun adviezen omtrent modificaties aan aminozuren en voor het 'lenen' van allerlei aminozuren Dr Q Broxterman (DSM) wordt bedankt voor het meerdere malen verstrekken van een monster *L* homofenylalanine Dr Ton Klunder en Dr Gordon Chittenden ben ik erkentelijk voor het corrigeren van het manuscript

De deskundige leden van de IOP-begeleidingscommissie Prof Dr P van Leeuwen (UvA), Prof Dr G van Koten (RUU), Dr M Groen (Organon), Dr L Hulshof (DSM Andeno), Dr J Douwstra (Solvay Duphar) en Prof Dr B Feringa (RUG) en Drs Joop Knol (RUG) worden bedankt voor hun stimulerende discussies tijdens de IOP-bijeenkomsten Dr Lucio Minuti (Universiteit van Perugia, Italie) wordt bedankt voor zijn adviezen omtrent cycloadditiereacties aan cyclohexenonen De gastvrijheid van Prof Dr Hisashi Yamamoto en Dr Arnel Concepcion (Universiteit van Nagoya, Japan) tijdens een bezoek aan Nagoya werd zeer op prijs gesteld

Ontspanning op z'n tijd is essentieel voor het welslagen van een spannend onderzoek Het voetballen ("in de wei rennen") bij de Trekvogels zaterdag 1 en 10, en muziek maken ("gitaar scheuren") bij Kinky Ribbon, vormden een aangename afleiding ' Bedankt voor het spelen !"

Jean-Paul

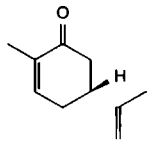
Contents

CHAPTER 1

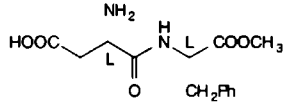
Chiral Lewis Acid Catalysts in Asymmetric Synthesis

1.1 General introduction

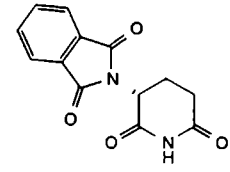
Non-racemic chiral molecules play an important role in the context of biological activity[1] Biological systems, in most cases, recognize the members of a pair of enantiomers as different substances, and the two enantiomers will elicit different responses For example, our senses of taste and smell are highly sensitive to subtle stereochemical differences in molecules that stimulate them A classic illustration is our olfactory response to the enantiomeric forms of the terpene carvone (*R*) Carvone has the odor of spearmint, whereas (*S*)-carvone smells like caraway The dipeptide ester aspartame has gained an increasing market share as a low-calorie sweetener and is used extensively in soft drinks Its backbone is composed of two amino acids, L-aspartic acid, which has no taste, and L-phenylalanine, which is bitter Together they form a molecule with intensely sweet taste characteristics (approximately 160 times sweeter than sucrose) Substitution of the L-phenylalanine portion of the molecule with its antipode D-phenylalanine, which in itself is sweet tasting, causes the resulting dipeptide ester to taste bitter



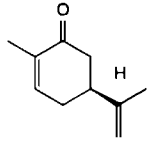
(*R*)-Carvone



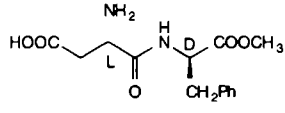
Aspartame sweet



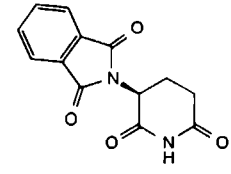
(*R*)-Thalidomide



(*S*) Carvone



bitter



(*S*)-Thalidomide

Less innocent effects appear when one enantiomer acts as a very effective therapeutic drug whereas the other enantiomer is either totally inactive or highly toxic The sad example of thalidomide is well known The racemic drug thalidomide sold as a powerful tranquilizer in the 1960s was

prescribed with catastrophic consequences because only the (*R*)-isomer serves as a tranquilizer while the (*S*)-isomer is shown to cause teratogenic effects in fetal development According to a recent report, more than 50% of the commercial drugs available worldwide have stereogenic centers Recent rulings of the Food and Drug Administration (FDA) in the United States clearly reflect the current situation in chiral drugs pharmaceutical industries will have to provide rigorous justification to obtain the FDA's approval of racemates Recently, chiral substances are also finding non-biological applications in material science such as electronics and optics The importance of asymmetric synthesis as a tool to obtain enantiomerically pure or enriched compounds has been fully acknowledged by chemists in synthetic organic, medicinal, agricultural, natural products chemistry and in the pharmaceutical and agricultural industries[2]

There are essentially four ways to obtain optically pure organic compounds[3] 1) resolution of the racemic mixture, 2) fermentation technology, 3) chiral auxiliaries/ chiral pool synthesis (chiral starting materials such as carbohydrates, amino acids, hydroxy acids and terpenes), and 4) the use of chiral catalysts Resolution of racemates is often the method of choice for the production of optically pure compounds on an industrial scale despite its low-technology image An increasing number of drugs, food additives and flavoring agents are being prepared by total synthesis In general, these compounds are obtained optically pure by means of an optical resolution performed at the end of the synthetic sequence This is a wasteful procedure because half of the synthetic product is often discarded It is economically and esthetically appealing to exclude unwanted optical isomers at the earliest possible stage through asymmetric creation of chiral centers and to consider carefully the principles of convergent synthesis

The ultimate goal of the exploration of new asymmetric processes is the development of methods to prepare chiral molecules as single enantiomers, preferably in large quantity and with a small number of synthetic and purification steps In an asymmetric reaction, substrate and reagent combine to form diastereomeric transition states One of the two reactants must have a chiral center to induce asymmetry at the reaction site Most often asymmetry is created upon conversion of trigonal carbons to tetrahedral ones at the site of the functionality, involving groups such as carbonyl, enamine, enol, imine and olefin By far, the best asymmetric synthesis is done in nature by enzymes However, a considerable effort has been put forward by chemists to achieve comparable results There is the challenge to develop chemical systems as efficient as enzymatic ones For a long time it was questioned whether high optical yields could be effectively attained by organic chemists without the help of enzymes However, an increasing amount of recent results demonstrates that versatile and efficient non-enzymatic asymmetric syntheses are indeed possible

Among the types of asymmetric reaction, the most desirable and the most challenging is catalytic asymmetric synthesis, since one chiral catalyst ("chemzyme") can create millions of chiral product molecules, just as enzymes do in biological systems Catalytic asymmetric synthesis often has significant economic advantages over stoichiometric asymmetric synthesis of enantiomerically pure compounds on industrial scale Enantioselective catalysis offers notable advantages over other conventional methods in that tedious and wasteful resolution procedures are not required, inefficient sequences involving attachment/detachment of chiral auxiliaries are not necessary, and

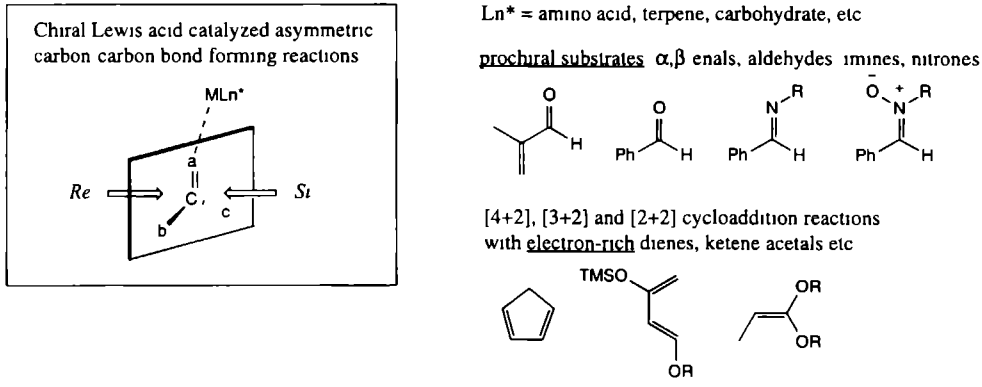
the process is not limited to the availability of starting materials from the chiral pool with structures similar to the desired target and with proper absolute configuration In fact, a number of catalytic asymmetric reactions, including the "Monsanto process" (asymmetric hydrogenation), the "Takasago process" (asymmetric isomerization), the "Sumitomo process" (asymmetric cyclopropanation), and the "Arco process" (asymmetric Sharpless epoxidation) were commercialized in the 1970s and the 1980s

1.2 Chiral Lewis acid catalysis

Asymmetric syntheses catalyzed by chiral Lewis acids[4], with central metal atoms, i e aluminum, titanium, boron, tin, lanthanides and others, have rapidly gained significant attention in the synthetic community, and these processes have a very high potential for commercial applications, especially in pharmaceutical and "chirotechnology" industries Chiral Lewis acid catalysts are employed in a series of important asymmetric carbon-carbon bond forming reactions These include Diels-Alder and ene reactions, Michael and aldol additions, and the addition of allyl and enol silanes and trimethylsilyl cyanide to aldehydes

The primary role of the Lewis acid is to activate a carbonyl function by complex formation The Lewis acid-catalyzed reactions not only proceed more rapidly than their thermal counterparts but they are generally also more regio- and stereoselective In principle, it should be possible to introduce chiral Lewis acids as a way of obtaining chiral complexes with prochiral substrates (e g , α,β-enals, aldehydes, imines, nitrones) suitable for asymmetric synthesis (*Scheme 1*)

Scheme 1



Although the initial results at the end of the 1970s were not encouraging the attractive possibilities inherent in catalytic processes continued to stimulate interesting new experiments in this difficult field From the mid 1980s the number of publications on chiral Lewis acid catalysis in asymmetric syntheses increased exponentially every year Significant advances have been made in terms of

substrate-catalyst interactions and the chiral recognition of substrate structures The rational design of a chiral catalyst that brings about extremely high enantioselectivity without the assistance of a huge protein backbone has now become within reach of synthetic organic chemists

1.3 Objectives of this study

For many reasons, the innovative pharmaceutical industry will continue to require facile synthetic routes to diastereomerically and enantiomerically pure chiral molecules In order to achieve these goals, new asymmetric processes, especially catalytic asymmetric reactions, will be needed The mission-oriented research described in this thesis was therefore financially sponsored by the Innovation Oriented research Program (IOP) on Catalysis of the Netherlands Ministry of Economic Affairs The objective of this study is the design, synthesis and testing of chiral Lewis acid catalysts for the asymmetric Diels-Alder reaction and related cycloadditions for the preparation of important chiral compounds for the innovative pharmaceutical industry (see *Scheme 1*) The additional advantage of catalytic asymmetric cycloaddition reactions, i e Diels-Alder, hetero-Diels-Alder, 1,3-dipolar, is that in a single step more than one new stereogenic center can be produced in a generally more regio- and stereoselective manner than under non-catalyzed conditions For this study electron-rich dienes and ketene acetals will be used

The use of chiral Lewis acid catalysts must satisfy most of the criteria for a good catalytic asymmetric synthesis, *viz* (i) high enantiomeric and chemical yields using catalytic amounts of a chiral catalyst, (ii) easy separation of the chiral products from the chiral catalysts, (iii) capability to synthesize both the enantiomers of the product, (iv) ready availability and low cost of the chiral ligands and (v) recovery of the chiral catalysts or chiral ligands

The academic and application-oriented industrial importance of detailed mechanistic studies for accurate understanding of asymmetric induction steps as well as key catalytic species is emphasized, since these studies will be essential for future breakthroughs in catalytic asymmetric synthesis and for commercial applications

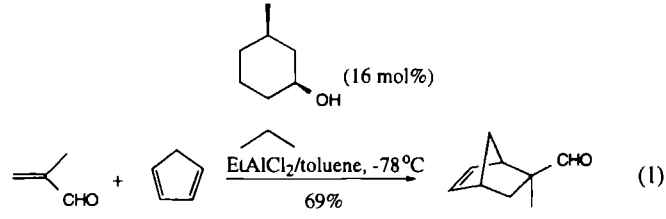
1.4 Literature survey

Recently, excellent reviews and books have appeared in the literature concerning the application of chiral Lewis acid catalysts in organic synthesis, especially in asymmetric Diels-Alder reactions In this section a summary of the literature reports is given on chiral Lewis acid catalyzed asymmetric carbon-carbon bond forming reactions subdivided by their different central metal atoms in the catalyst, i e aluminum, titanium, boron, lanthanide and others published up to January 1995 It is not the purpose to cover all examples that have already been described in review articles, but some of those will be presented because of their general relevance for asymmetric synthesis The asymmetric hydroboration of olefins with chiral boranes and the asymmetric reduction of ketones with chiral oxazaborolidines have been reviewed elsewhere[3r,s] and will not be discussed because these reactions do not fit within the framework of this thesis

1.4.1 Chiral Aluminum Catalysts

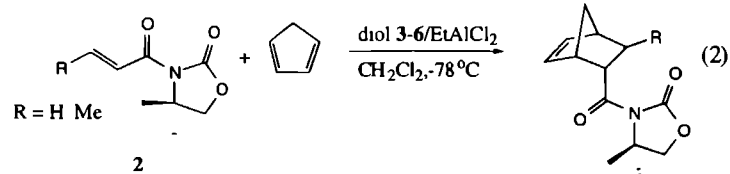
Chiral aluminum catalysts have been applied in various synthetic reactions, e g the asymmetric Diels-Alder reaction of α,β-unsaturated mono- and bidentate dienophiles with simple dienes, the asymmetric hetero Diels-Alder reaction of aldehydes, the asymmetric ene reaction and the asymmetric Claisen rearrangement

In 1979 Koga *et al* described menthoxyaluminum dichloride as a chiral Lewis acid catalyst in the Diels-Alder reaction of methacrolein and cyclopentadiene. An enantiomeric excess of 72% was realized for the *exo*-cycloadduct **1**[5a] (eq 1) There was no further report in that area until 1987 when the same authors confirmed their own results (the enantiomeric excess was revised to 57% ee) for the cycloadduct **1** and proposed an interpretation based on the absolute configuration of the reaction product[5b] Valenta *et al* found with the same chiral aluminum catalyst similar enantioselectivity in asymmetric Diels-Alder reactions of cyclopentadiene with conformationally rigid α,β-unsaturated ketones[6]



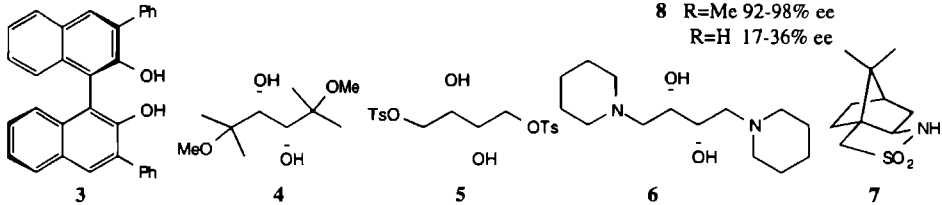
1 57 % e e

The chiral aluminum chloride generated similarly from ethylaluminum dichloride and chiral diols **3-6** (in a 2 1 ratio) and sulfonamide **7** (in a 1 1 ratio), studied by Chapuis *et al* exhibited high enantioselectivity in the asymmetric Diels-Alder reaction between acryloyl- and crotonoyl-oxazolidinone **2** (R=H, Me) and cyclopentadiene[7] (eq 2)



2

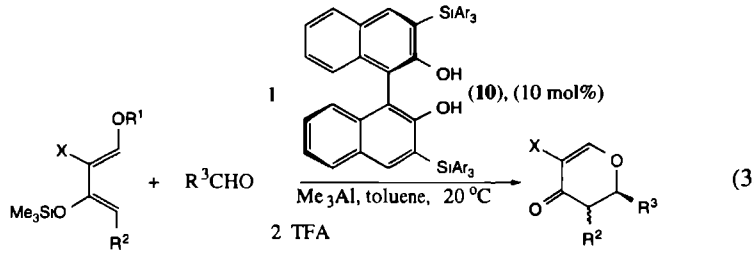
8 R=Me 92-98% ee
R=H 17-36% ee



3 **4** **5** **6** **7**

However, synthetic application has been rather limited, since the chiral aluminums could only be employed succesfully as stoichiometric reagents and only for crotonoyl dienophile **2** (R=Me) Attempted cycloaddition with the acryloyl analog of **2** (R=H) resulted in a marked loss of enantioselectivity for **8** (17-36% ee)

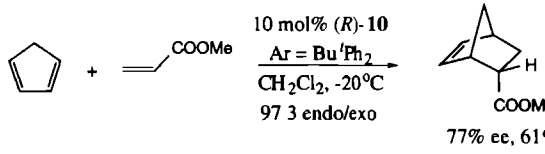
The asymmetric hetero Diels-Alder reaction between some derivatives of the Danishefsky diene **9** and aldehydes was investigated by H. Yamamoto *et al* The reaction was found to be accelerated by chiral aluminum species generated from (*R*)-3,3'-bis(triarylsilyl)binaphtol **10** and trimethylaluminum resulting in the formation of dihydropyrones **11** with high enantioselectivity[8] (eq 3a) Enantiofacial differentiation of prochiral aldehydes could be controlled by fine-tuning the size of the trialkylsilyl moiety in **10** The enantioselective activation of carbonyl groups with the bulky chiral aluminum (*R*)-**10** or (*S*)-**10** was further applied in the asymmetric ene reaction of electron-deficient aldehydes with various alkenes in the presence of powdered 4Å molecular sieves[9], in the asymmetric Claisen rearrangement of allylic vinyl ethers,[10] and in the asymmetric Diels-Alder reaction of cyclopentadiene and methyl acrylate (eq 3b)[11]



(3a)

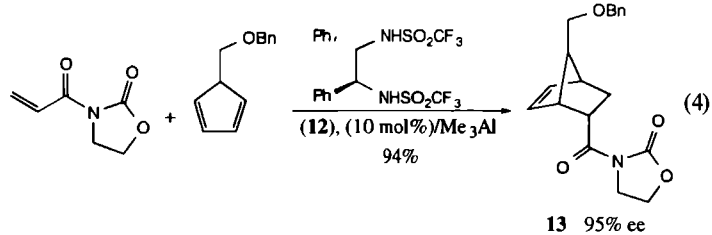
9
X = H, OAc, Me
R^1 = Me_3Si, Me
R^2 = H, Me

11a Ar = Ph, 67-95% ee
11b Ar = 3,5 xylyl, 81-97%ee



(3b)

A highly selective asymmetric Diels-Alder reaction was reported by Corey *et al* who prepared chiral aluminum complexes derived from chiral bis-sulfonamides **12** with C_2 symmetry[12] (eq 4). The aluminum complex (0.1 mol equiv) acts as a catalyst for the cycloaddition between 3-acryloyl-1,3-oxazolidin-2-one and cyclopentadienes, giving a useful intermediate **13** for the production of optically active prostaglandins

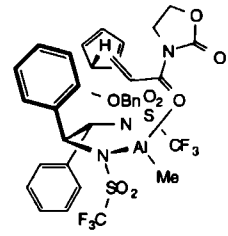


(4)

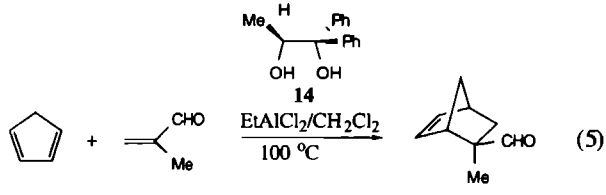
13 95% ee

A transition-state assembly (Chart 1 1) was suggested for the formation of **13**, based on X-ray crystallographic and NMR studies on the structure of the catalyst and on the catalyst-dienophile complex in solution [12c]

Chart 1 1

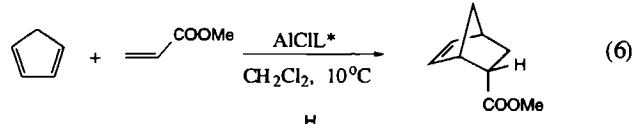


Kagan *et al* investigated the Diels-Alder reaction catalyzed by aluminum alcoholates of chiral C_2 diols or monoethers of chiral diols at -78 °C Most diols gave disappointing results, except 1,1'-diphenyl-1,2-propanediol **14** (eq 5)[13] Various experimental parameters of the reaction were studied, e g dienophile/catalyst ratio, aging of the catalyst, and temperature The enantioselectivity was optimized to 86% ee at -100 °C

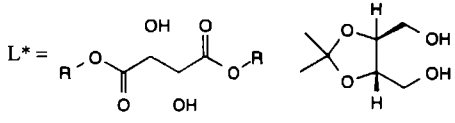


86% ee, 90%

Many dialkoxychloroaluminum complexes were studied by Herrmann *et al* who also showed the influence of aging time on the composition of the catalyst solution (eq 6)[14] It was shown by ^{27}Al-NMR and cryoscopic measurements that formation of a dimer from a monomer was fast at room temperature, but in the presence of a dienophile like methyl acrylate, the dimerization process became very slow The asymmetric Diels-Alder reaction between methyl acrylate and cyclopentadiene was performed with various chiral bidentate ligands Ee's up to 70% were achieved

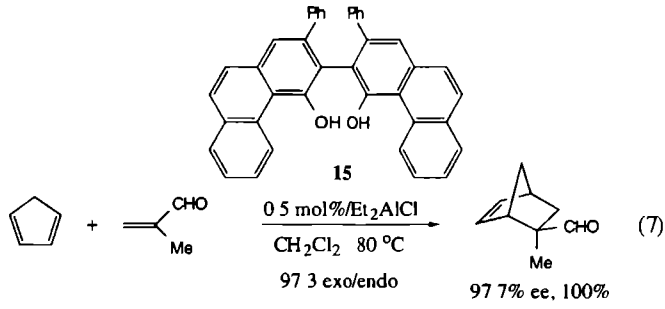


a 70% ee, 49%
b 40% ee, 41%



a R= c C_6H_{11} **b**

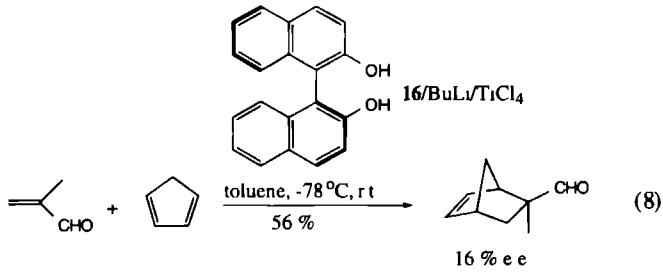
Vaulted biaryls as chiral ligands were designed by Wulff *et al* for the catalytic asymmetric Diels-Alder reaction between methacrolein and cyclopentadiene (eq 7)[15] The vaulted biphenanthrol (VAPOL) **15** is believed to form a chiral pocket, the active site of the catalyst being in the concave portion of the molecule The enantioselectivity was shown to be dependent on the aging time of the catalyst and on the concentration of the dienophile and its ratio to the catalyst With 0 5 mol% catalyst an enantiomeric excess of 97 7% was achieved in 4 hrs at -80 °C, the highest induction and lowest catalyst loading reported for any catalytic asymmetric Diels-Alder reaction until 1993



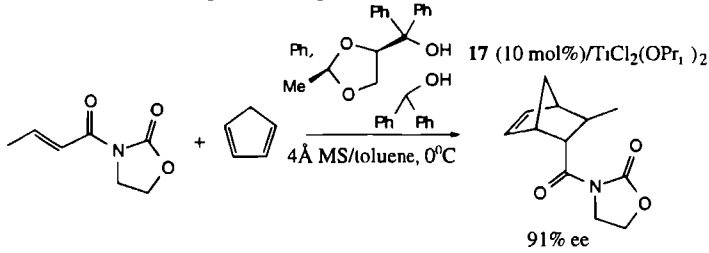
1.4.2 Chiral Titanium Catalysts

Several types of chiral titanium reagents have been developed for different asymmetric C-C bond forming reactions, including the inter- and intramolecular Diels-Alder, hetero Diels-Alder, [2+2]-cycloaddition, ene, aldol-type and alkylation reactions as well as cyanohydrin formation

Stoichiometric amounts of titanium complexes were first utilized[16], followed by catalytic approaches Reetz *et al* succesfully prepared the monomeric dichlorotitanium complex **16** by treatment of the dilithio derivate of (*S*)-binaphtol with titanium tetrachloride The asymmetric Diels-Alder reaction of cyclopentadiene and methacrolein at -78 °C afforded the *exo* adduct with only 16% ee (eq 8)[17] However, the same reagent effects an asymmetric cyanohydrin formation in high yield and e e 's up to 82%

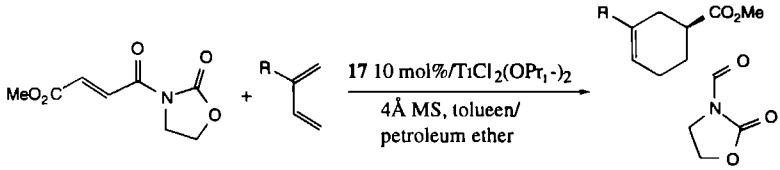


Narasaka *et al* found that a class of crotonamides (3-acyl-1,3-oxazolidin-2-ones) reacts with cyclopentadiene to give cycloadducts with up to 91% enantiomeric excess in the presence of a catalytic amount of titanium complex **17** (eq 9)[17]



The catalyst is prepared by mixing the chiral diol **15** and $TiCl_2(OPr\text{-}i)_2$ at room temperature in the presence of 4Å molecular sieves Without 4Å molecular sieves stoichiometric amounts of titanium complex (2 eq) were needed to obtain equal enantioselectivity[16a] The same authors found a

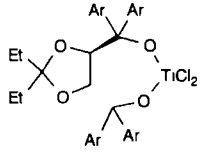
remarkable solvent effect in this catalytic reaction Various cycloadducts were obtained in high optical yields in mesitylene, chlorofluorocarbons and a mixture of toluene and petroleum ether[18] For example, 4-methyl-4-cyclohexenedicarboxylate derivative **18** was produced with 91-94% ee by the action of 10 mol% of the chiral titanium reagent **17** in the presence of 4Å molecular sieves (eq 10)



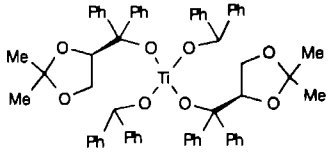
R = Me H **18** 91 94% ee

The reaction has been extended to a diene containing a sulfur atom, such as 2-(ethylthio)-1,3-butadiene, affording the Diels-Alder adduct in 91% ee[19a] The reaction was also modified to proceed as an intramolecular Diels-Alder reaction, where the bicyclic cycloadduct (>95% e e) is transformed into the hydronaphtalene moiety of mevinic acid[19b] Furthermore, the chiral titanium reagent **17** was succesfully applied to asymmetric [2+2] cycloadditions[19c], ene reactions[19d], cyano hydrin formation[19e] and asymmetric solvolysis of racemic *S*-(2-pyridyl) thioesters of α-arylcarboxylic acid[19f] High asymmetric induction was observed in all cases

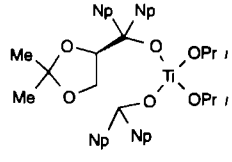
Corey *et al* investigated modified titanium catalysts and improved the asymmetric Diels-Alder reaction of Narasaka Upon studying various analogs of **17** in which the phenyl groups of the tertiary carbinol subunit are replaced by other aromatic groups with variable π-basicity, they found that the use of 3,5-xylyl groups in **19** gave the best results The asymmetric cycloaddition of 5-((benzyloxy)methyl)-1,3-cyclopentadiene with N-acryloyl-1,3-oxazolidin-2 one (eq 4) was carried out in the presence of a catalytic amount of **19** (Ar= 3,5-xylyl) in toluene at 30 °C producing the cycloadduct **13** with 95% ee[20] It was proposed that attractive π-π interactions between a donor aromatic group and the double bond of the dienophile shield one face, which leads to high enantioselectivity Structurally related titanium complexes **20** and **21** have been applied by Seebach *et al* to the asymmetric alkylation of benzaldehyde with diethylzinc, producing (*S*)-1-phenyl-1-propanol **23** with high enantioselectivity[21]



19

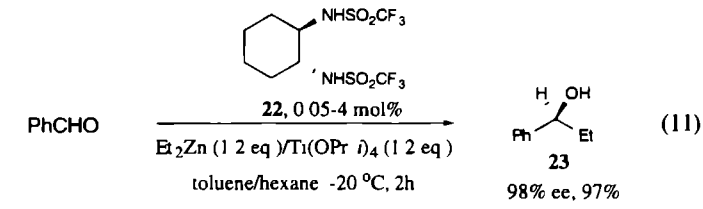


20



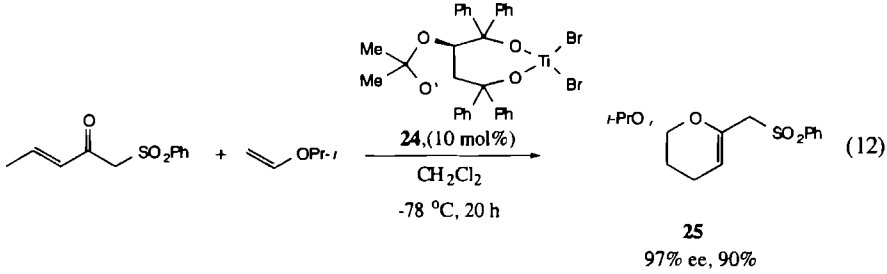
21

A chiral titanium catalyst derived in situ from (*R*)-*bis*(trifluoromethanesulfonamide) **22** and titanium tetraisopropoxide was developed by Ohno *et al* The introduction of the chiral sulfonamide auxiliary onto titanium increased the Lewis acid activity and markedly accelerated the same alkylation reaction (eq 11)[22]



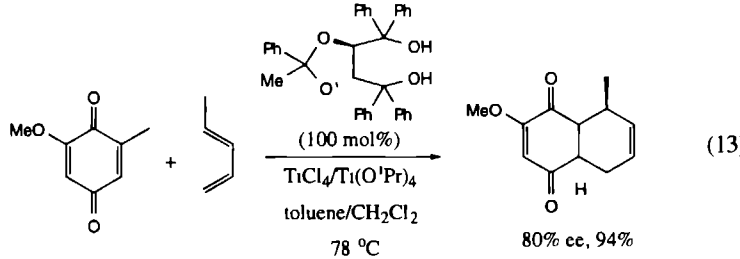
(11)

Wada *et al* found that the asymmetric hetero Diels-Alder reaction of (*E*)-2-oxo-1-phenylsulfonyl-3-alkenes with vinyl ethers was effectively activated by a catalytic amount of chiral titanium reagent **24**, prepared from a chiral diol and $TiBr_2(OPr\text{-}i)_2$ in the presence of 4Å molecular sieves (eq 12)[23] The cycloadducts, e g dihydropyran **25**, were obtained in high yield with excellent *endo*- and enantio-selectivity In several steps the cycloadducts were transformed into chiral 3-substituted cyclohexanones, which are interesting chiral building blocks



(12)

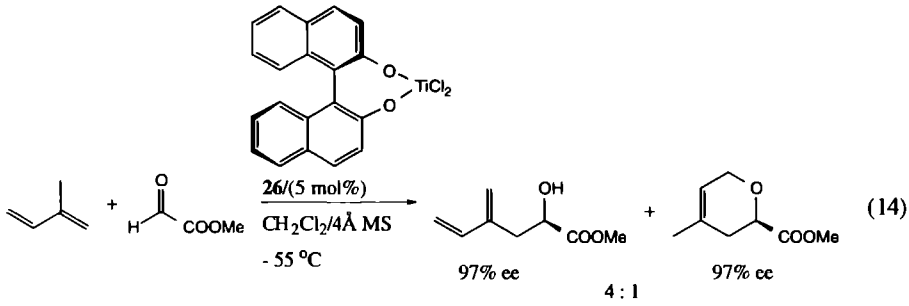
Recently, Engler *et al* demonstrated that the preparation method of the Ti(IV) reagent **17** has a dramatical influence on the regio- and enantioselectivity of quinone Diels-Alder reactions (eq 13)[24a] When the complex was prepared according to the procedures of Narasaka ($TiCl_2(O^iPr)_2$) or Corey, or from BuLi/$TiCl_4$, the reaction was found to be not as effective as when the complex was prepared from a 1 1 1 mixture of $TiCl_4$, $Ti(O^iPr)_4$ and the chiral diol Although the structure of the catalyst was not clarified, the Diels-Alder reaction of 2-methoxy-1,4-benzoquinones with simple dienes proceeded in high yields with enantioselectivities up to 80% ee The catalyst appeared to be also very effective for the asymmetric [2+2] cycloaddition of substituted styrenes and 1,4-benzoquinones[24b]



(13)

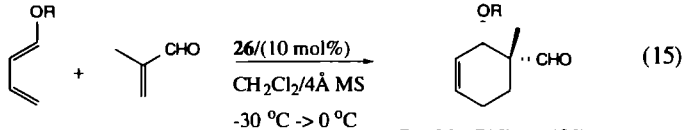
Mikami *et al* investigated various Diels-Alder and ene reactions catalyzed by the chiral titanium complex (*R*)-**26** (BINOL-Ti) prepared in situ from (*R*)-binaphtol and $TiCl_2(OPr\text{-}i)$ in the presence of 4Å molecular sieves The reaction between isoprene and methyl glyoxylate was catalyzed by 5 mol% **26** to give a mixture of the ene product and a hetero Diels-Alder product, both in very high

ee (eq. 14)[25a].



(14)

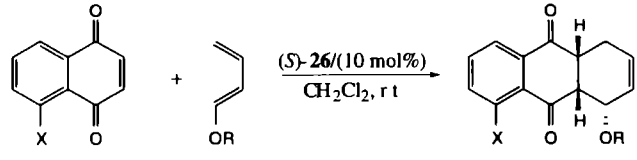
The use of this catalyst was extended to the asymmetric Diels-Alder reaction between 1,3-dienol derivatives and methacrolein or 1,4-naphtoquinone. The *endo* selectivity was high in most cases (eq. 15). The authors proposed that the steric course of the reaction is the result of complexation of methacrolein via its transoid conformation and the titanium catalyst being complexed in an *anti* fashion.



(15)

R = Me 71% ee, 43%
R = C(O)NMe$_2$. 86% ee, 82%

The chiral titanium catalyst **26** was succesfully applied by Mikami *et al.* in the asymmetric glyoxylate-ene reaction[26a-d], e.g. with vinylic sulfides and selenides[26d], the Mukaiyama aldol reaction with silyl enol ethers[26e], aldol-type reactions with ketene silyl acetals[26f] and the Sakurai-Hosomi reaction with allylic silanes[26g]. Recently, the same authors found that the use of molecular sieves is essential for the *in situ* preparation of the chiral catalyst **26**, but also has dramatic effects on the enantioselectivity of Diels-Alder reactions[27]. The enantioselective Diels-Alder reaction of 5-hydroxynaphtoquinone (juglone) or methyl glyoxylate with 1,3-dienol ethers and esters was catalyzed by a chiral BINOL-Ti complex **26** which had been freed from the molecular sieves (MS).



(16)

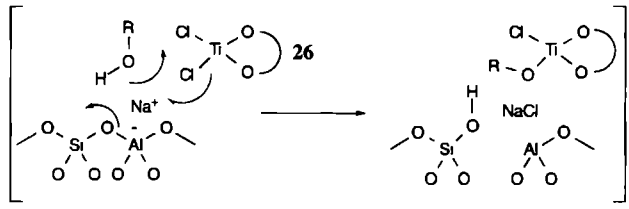
X =H, OH

R = COMe

X = H , + MS 85% ee
X = OH, + MS 9% ee
X = OH, - MS · 76-96% ee

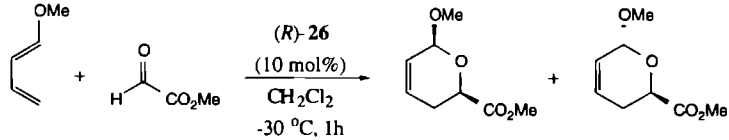
In the presence of 4Å MS, the reaction of juglone with butadienyl acetate, for example, was catalyzed by 10 mol% (*S*)-**26** to give the cycloadduct with only 9% ee. However, under MS-free conditions the enantioselectivity was enhanced to 76-96% ee (eq. 16). The low enantioselectivity (9% ee) is in marked contrast to the 85% ee obtained for the parent naphtoquinone (X=H). This indicates that in the presence of MS the free hydroxy group in juglone (X=OH) binds to titanium,

displacing chloride as shown in eq 17 The MS is assumed to catalyze the reaction of juglone with the diene which explains the low enantioselectivity



(17)

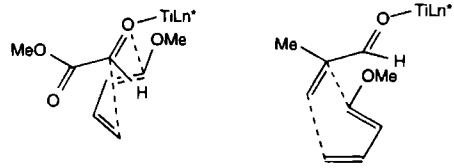
The use of MS-free complex **26** also improved the *endo*-selectivity and enantioselectivity in the hetero Diels-Alder reaction of methyl glyoxylate with methoxydienes and provided a useful chiral intermediate (96% ee) for the synthesis of monosaccharides and the lactone portion in mevinolin or compactin (coenzyme A reductase inhibitors) (eq 18)



(18)

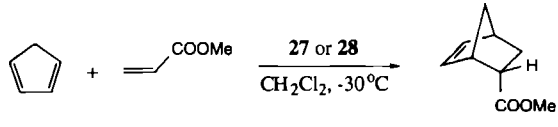
The sense of asymmetric induction, as observed in Diels-Alder reactions with the enal in eq 15 was exactly the same as found in the glyoxylate-ene reactions and hetero Diels-Alder reactions with glyoxylate Therefore, the authors proposed transition states for the hetero Diels-Alder reaction with methyl glyoxylate and the Diels-Alder reaction with methacrolein in which the titanium is complexed in an *anti* fashion and the reactions proceed through an *endo*-transition state (Chart 1 2)

Chart 1 2



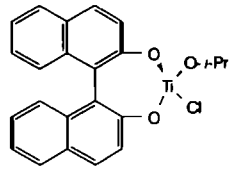
anti endo *anti-endo*

Chiral monochlorotitanium reagents **27** and **28**, which are derived in situ from chlorotitanium triisopropoxide and the corresponding chiral diols by azeotropic removal of isopropanol, were found by Seebach *et al* to exhibit a moderate asymmetric induction (42-50% ee) in the asymmetric Diels-Alder reaction of cyclopentadiene and methyl acrylate (eq 19)[28].

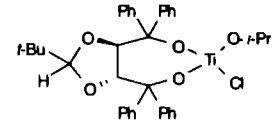


(19)

50% ee (77%) with **27**
42 46% ee (55-74%) with **28**

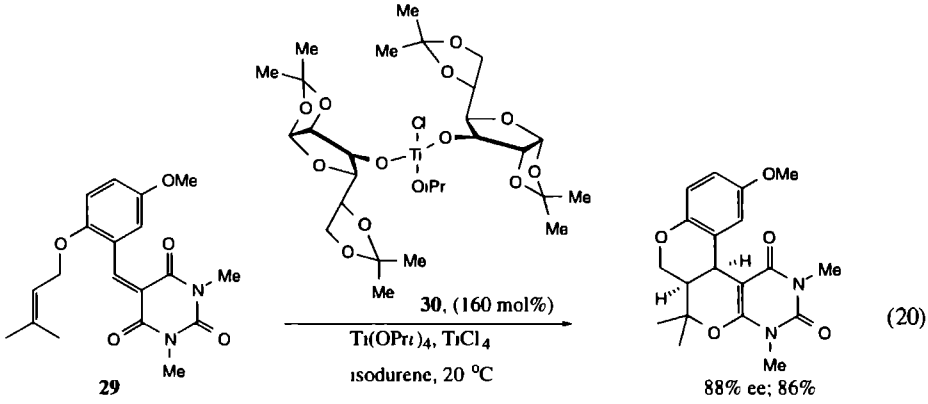


27



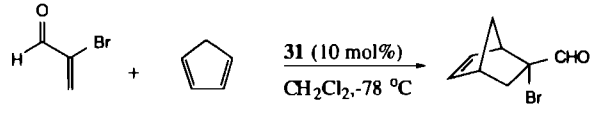
28

Tietze *et al.* examined the intramolecular hetero Diels-Alder reaction of 1-oxa-1,3-butadienes **29**, obtained in situ by a Knoevenagel condensation of aromatic aldehydes and N,N'-dimethylbarbituric acid, in the presence of a chiral monochlorotitanium Lewis acid **30** with a protected glucofuranose (diacetone glucose) as ligand (eq. 20)[29]. The catalyst was prepared in situ by reaction of titanium tetraisopropoxide, titanium tetrachloride and diacetone glucose in a ratio of 3:1:8. The cycloadducts were obtained with enantioselectivities up to 88% ee after 36 hours reaction time at room temperature. The solvent had a dramatic effect on the enantioselectivity, i.e. toluene and isodurene gave best results in contrast to dichloromethane (52% ee), THF (25% ee) or chloroform (0% ee).



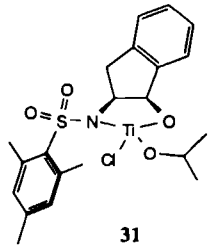
29 (20)

Corey *et al.* obtained the monochlorotitanium complex **31** from (*1R,2S*)-N-(2,4,6,-trimethyl-benzenesulfonyl)-2-amino-1-indanol and titanium tetraisopropoxide followed by treatment with $SiCl_4$. This catalyst appeared to be a more reactive catalyst than the diisopropoxy analog obtained initially. The Diels-Alder reaction of 2-bromoacrolein and cyclopentadiene was catalyzed by 10 mol% of **31** at -78 °C to afford the *exo*-cycloadduct with 93% ee (eq. 21)[30].

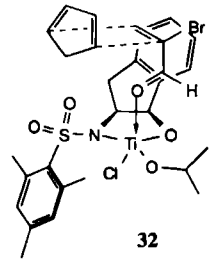


93% ee, exo/endo 67·1 (21)

For this reaction the transition-state assembly **32** was proposed, in which attractive π-π interactions between the indane ring system and the complexed *s-cis* aldehyde, which have a parallel orientation, are assumed to control the enantioselectivity.

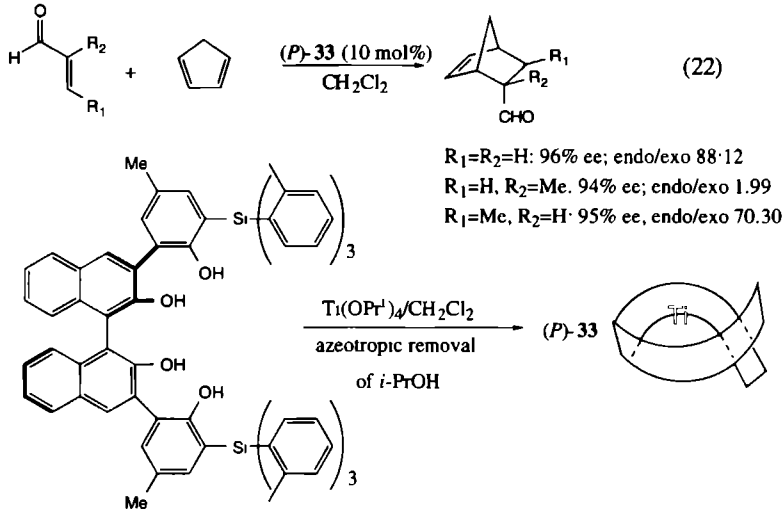


31

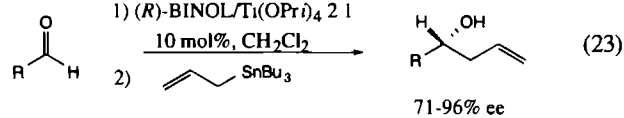


32

Recently, Yamamoto *et al.* prepared chiral helical titanium reagents of type (*P*)-**33** (*P* denotes "right-handed" helical conformation) derived from titanium tetraisopropoxide and a chiral ligand derived from optically pure *R*-binaphtol. These reagents were succesfully utilized as a chiral template for achievement of uniformly high asymmetric induction in asymmetric Diels-Alder reactions with dienes, regardless of temperature (eq 22)[31]. Such temperature effect is in contrast to most of the known metal-catalyzed asymmetric reactions, where the enantioselectivity is enhanced by lowering the temperature[4a,b].

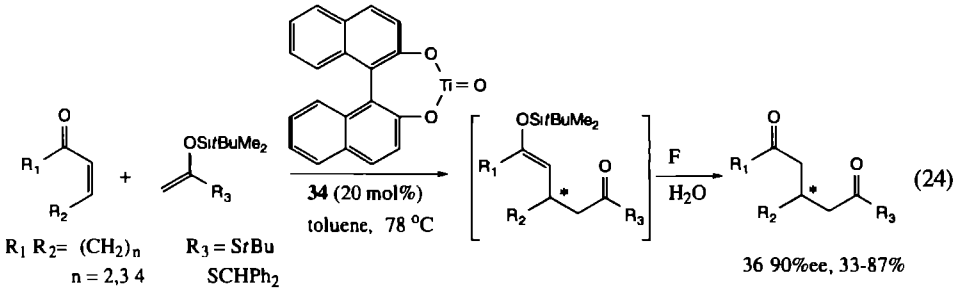


Keck *et al.* studied the catalytic asymmetric allylation reaction of aldehydes using allyltri-*n*-butylstannane and a chiral titanium catalyst (10 mol%) prepared from (*R*)-BINOL and titanium tetraisopropoxide in a 2:1 ratio (eq.23)[32]. The allylation reaction gave the product alcohols with prevalent *R* configuration in high enantiomeric excess.



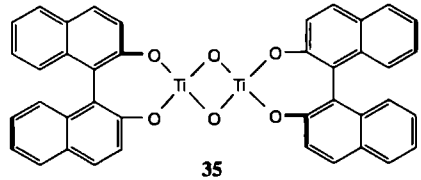
R=Ph, $PhCH_2CH_2$, furyl, C_6H_{11}

Kobayashi *et al* developed a catalytic asymmetric Michael reaction of silyl enol ethers with α,β-unsaturated ketones using a chiral titanium oxide **34** (eq 24)[33] The corresponding Michael adducts were obtained in high yields with moderate to high enantiomeric excesses



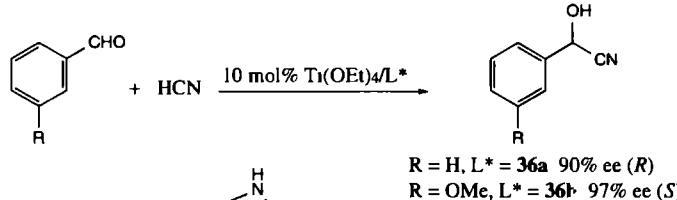
(24)

Recently, Nakai *et al* prepared a related titanium complex **35** with a μ-oxo dimer backbone, by complete hydrolysis of a binaphtol-derived diisopropoxytitanium complex, which was succesfully applied in the asymmetric glyoxylate-ene reaction with very high enantiomeric excesses[34]

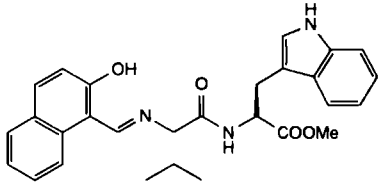


35

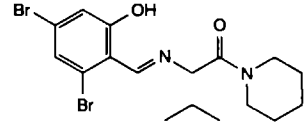
Inoue *et al* found reverse enantioface selectivities in the asymmetric hydrocyanation of aldehydes catalyzed by equimolar amounts of titanium complexes derived from $Ti(OEt)_4$ and dipeptide esters **36a** and **36b** in which the terminal amino groups were derivatized as a Schiff base (eq 25)[35] The mandelonitrile derivatives were obtained with high enantioselectivities The titanium complexes were further used in the asymmetric epoxidation of allylic alcohols with enantioselectivities up to 66% ee[36a]



(25)



L* **36a**



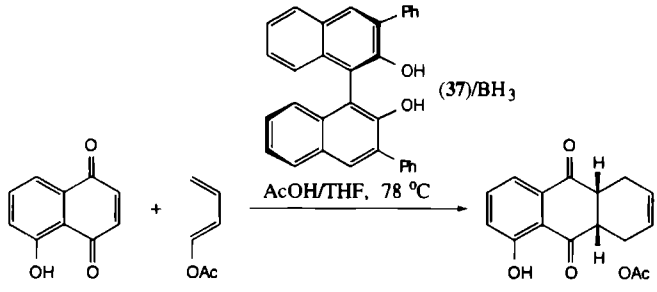
36b

Similar peptide-aluminum complexes[36b], derived from dipeptide esters and trimethylaluminum, and chiral sulfoximine/titanium complexes[36c] were applied as chiral Lewis acids both in stoichiometric and catalytic amounts, in the asymmetric addition of cyanotrimethylsilane (TMSCN) to aldehydes, affording cyanohydrins with moderate enantioselectivities

1.4.3 Chiral Boron Catalysts

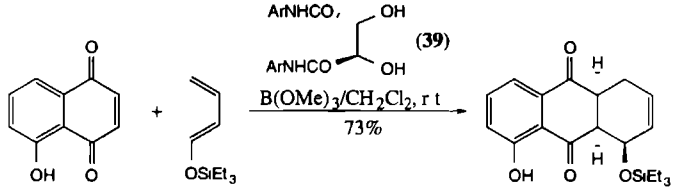
Chiral boron catalysts have been widely used as Lewis acids in the asymmetric reduction of C=O and C=N bonds, Diels-Alder, hetero Diels-Alder, ene, Mukaiyama aldol, Sakurai-Hosomi allylation, aldehyde hydrocyanation, and dialkylzinc addition reactions[3e]

Chiral boron compounds were first explored in stoichiometric amounts as promoters for the Diels-Alder reaction of quinones with electron-rich dienes in the preparation of intermediates for tetracycline systems Kelly *et al* found that the Diels-Alder reaction of juglone with acetoxybutadiene in the presence of stoichiometric amounts of chiral boron catalyst, prepared from BH_3, acetic acid and 3,3'-diphenylbinaphtol **37** yielded the cycloadduct **38** with 98% ee (eq 26)[37] The reaction proceeds via a spirocyclic borate complex, in which one face of the double bond in juglone is effectively shielded from attack of the diene



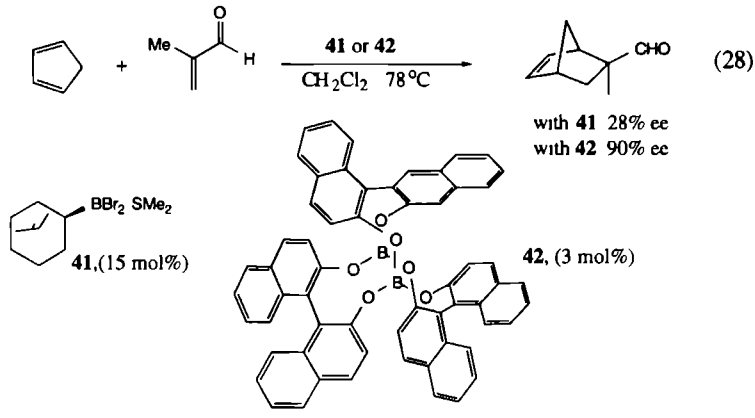
38 >98% ee (26)

A similar approach was followed by H Yamamoto *et al* (eq 27)[38] A chiral boron reagent which was prepared from trimethyl borate and various (*R,R*)-tartaric acid diamides **39** effectively catalyzed the asymmetric Diels-Alder reaction of juglone with a silyloxydiene to give the cycloadduct **40** with high enantioselectivity

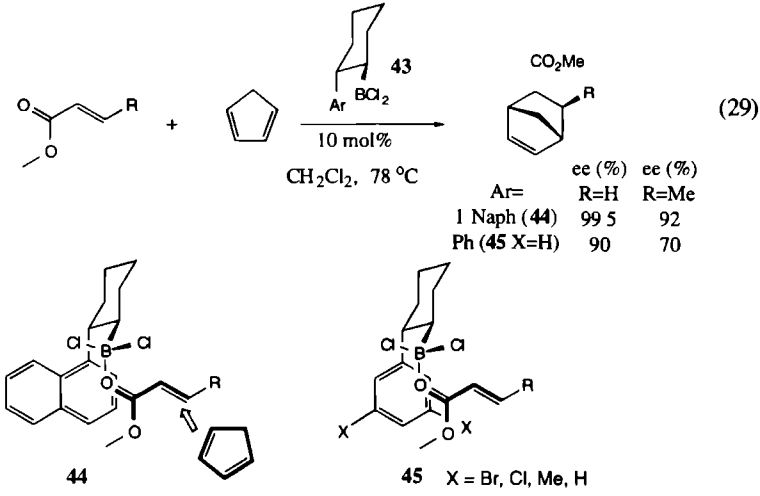


Ar = *m*-tolyl **40** 92% ee (27)

Kaufmann *et al* examined the catalytic asymmetric Diels-Alder reaction of cyclopentadiene with methacrolein mediated by chiral boron complexes **41** and **42**, derived from $HBBr_2$-SMe_2 and resp pinene[39] and binaphtol[40] (eq 28) A low ee was found for chiral boron complex **41** whereas the enantioselectivity was greatly improved by using chiral diborate **42** The structure of **42** was determined by X-ray analysis The molecule has a propeller-like shape with an interesting C_3 symmetry

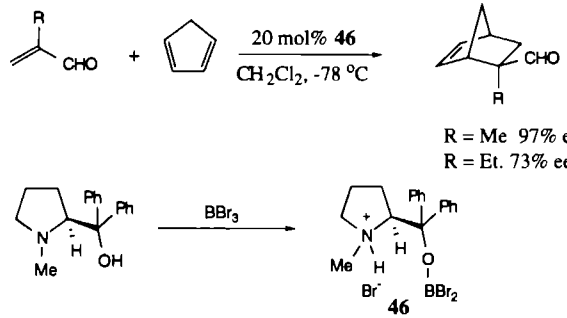


Hawkins *et al* described a simple and efficient catalyst (**43**) for the Diels-Alder reaction of methyl acrylates with cyclopentadiene (eq 29)[41] The chiral alkyldichloroborane **43** was prepared by hydroboration of the corresponding alkene followed by resolution A molecular complex between methyl crotonate and the chiral catalyst was isolated for the first time A crystal structure study of the complex allowed the authors to propose a mechanism for the reaction, see **44** The approach of the diene was suggested to occur on one of the faces of methyl crotonate because of protection of the other face by π-π donor-acceptor interactions This secondary attractive substrate-catalyst interaction[3g] also is the key to the stereocontrol of the reaction of methyl acrylate (R = H) with 5 eq cyclopentadiene, which proceeded with very high enantioselectivity (97% ee)



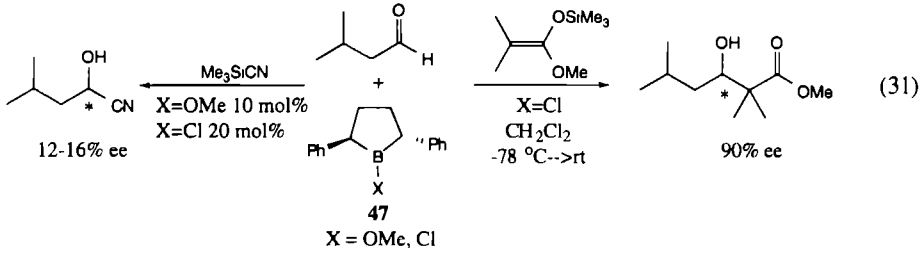
Three years later the same authors reported that in the presence of excess cyclopentadiene (10 eq) catalyst **44** gives the product with up to 99 5% ee[42] This two-point binding chiral recognition mechanism was also found for catalyst complexes **45** with various polarizable arene moieties The enhanced dipole-induced-dipole attraction between the substrate and the catalyst in the case of more polarizable catalysts, i e naphtyl (**44**) is considered to be more polarizable than phenyl (**45**), was proposed to explain the enhanced enantioselectivity

Kobayashi *et al.* prepared chiral boron reagent **46** from BBr_3 and a chiral prolinol derivative to give a Diels-Alder adduct with good to excellent asymmetric induction (eq. 30)[43].



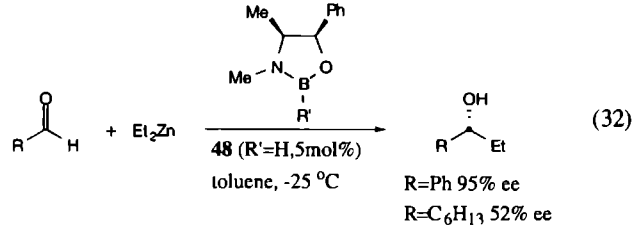
(30)

Reetz *et al.* found that chiral 1-boracyclopentyl chloride or methoxide **47** could be used as a catalyst in the hydrocyanation reaction and the aldol reaction of 3-methylbutanal with trimethylsilyl cyanide and a ketene silyl acetal, respectively (eq. 31)[44]. The enantioselectivity in the aldol reaction was high (90% ee), but stoichiometric amounts of **47** were needed. The hydrocyanation reaction proceeded with poor enantioselectivity but is the first example of chiral organoborane catalysis in this reaction type.



(31)

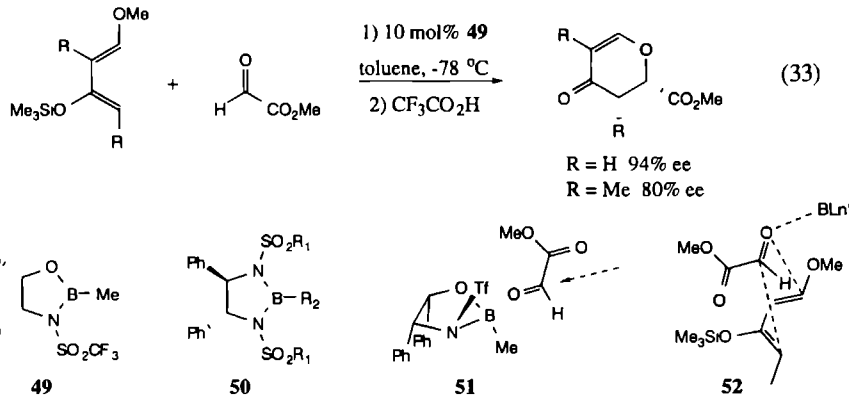
Brown *et al.* prepared chiral 1,3,2-oxazaborolidine **48** from a chiral amino alcohol and borane-dimethylsulfide or dialkoxyborane, and applied it in the asymmetric diethylzinc addition to aldehydes (eq. 32)[45].



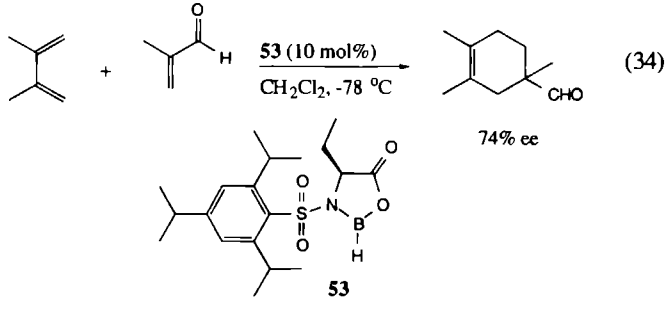
(32)

Mikami *et al.* developed a chiral amino alcohol derived boron complex (**49**) which gave high enantioselectivity (94% ee) in the asymmetric hetero Diels-Alder reaction between glyoxylate and Danishefsky dienes (eq. 33)[46]. Because moderate enantioselectivity (up to 62% ee for $R_1=CF_3$, $R_2=H$) was obtained with the bis-sulfonamide complexes **50** the authors proposed transition-state assembly **51** with a one-directional diene approach from the site proximal to the sulfonyl moiety to explain the high enantioselectivity observed for **49**. Furthermore, the boron catalyst **49** should be

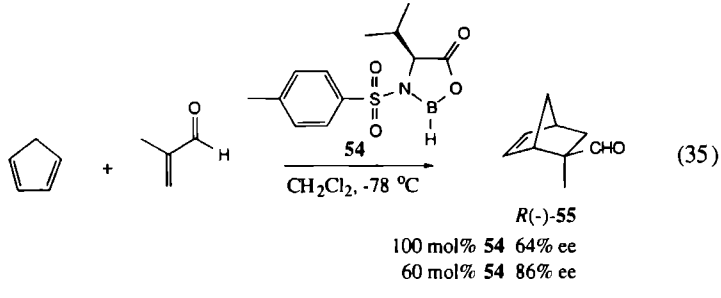
complexed to glyoxylate in an *anti* fashion and the Diels-Alder reaction should proceed with *endo*-orientation as presented by **52**



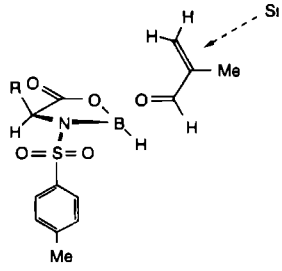
Yamamoto *et al* prepared simple chiral boron catalysts from sulfonamides of amino acids and borane, which were applied to the asymmetric Diels-Alder reaction of cyclopentadiene with various α,β-unsaturated aldehydes (eq 34)[47] The best result was found with chiral oxazaborolidine **53** in the asymmetric Diels-Alder reaction of methacrolein with 2,3-dimethylbutadiene to give 74% ee of the cycloadduct



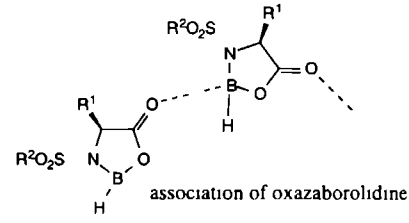
At the same time Helmchen *et al* independently found similar results with chiral oxazaborolidine **54** derived from the *p*-toluenesulfonamide of *L*-valine and borane-THF (eq 35)[48] With 100 mol% chiral boron complex **54**, the reaction of methacrolein with cyclopentadiene gave 64% ee of the product *R*(-)-**55**



The enantioselectivity was increased to 86% ee when 60 mol% **54** was used and it was shown that the presence of a donor solvent like THF was essential for obtaining high enantioselectivity[49] To explain the found configurational relationships, transition state model **56** was proposed, mainly based on (i) steric repulsive forces between substituent R and the arylsulfonyl part of the oxazaborolidine and (ii) computational studies from the literature which suggested a *s-cis*-enal complex as the preferred conformation Almost complete loss of enantioselectivity was found when the catalyst **54** was prepared from 1M BH_3-SMe_2 in CH_2Cl_2 It was suggested that in the acceptor solvent CH_2Cl_2, association of the catalyst *via* the carbonyl group (as depicted by **57**) decreases the enantioselectivity by shielding of the C_α-*Si* enal face in model **56**

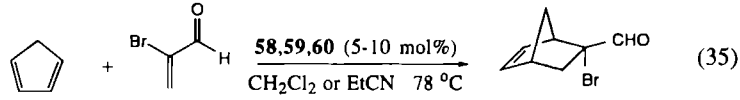


56



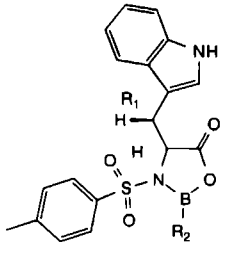
57

Remarkably, Corey *et al* reported that for this reaction catalyst **60** (5 mol%), derived from ($\alpha S,\beta R$)-β-methyltryptophan and *n*-butylboronic acid, gives complete reversal of enantioselectivity in dichloromethane yielding *S*(+)-**55** with e e up to 92% [51a] The asymmetric Diels-Alder reaction of 2-bromoacrolein with cyclopentadiene catalyzed by tryptophane-derived oxazaborolidines **58**, **59** or **60** gave the cycloadduct *R*-**61** with very high enantioselectivities up to 99% ee (eq 35)[50] It was noted that oxazaborolidines derived from e g *L*-valine gave the opposite enantiomer *S* **61** with moderate ee

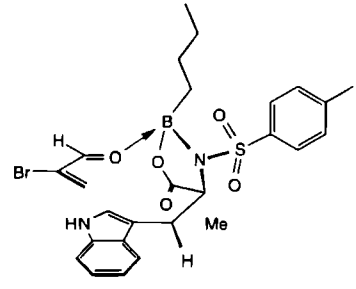


(35)

R-**61** 92-99% ee



58 R_1=R_2=H
59 R_1=H R_2=*n* Bu
60 R_1=Me R_2=*n* Bu

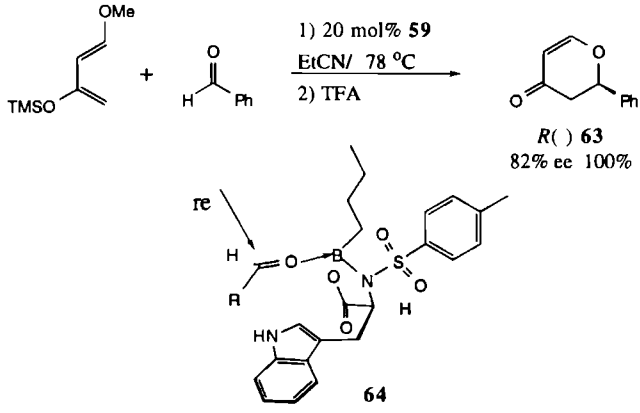


62

Based on NMR studies[51a b] the authors proposed transition state model **62** to explain the reversed enantioface selectivities Attractive π-π interactions between the indolyl moiety and the complexed

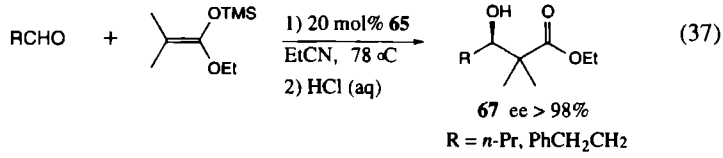
cis-enal are supposed to shield one enantioface, promoting attack of the diene to occur from the other side The Diels-Alder reaction of 2-bromoacrolein with furan was reported to be catalyzed by chiral boron catalyst **60** to give high enantioselectivities up to 92% ee[52] The corresponding catalysts **58** and **59** gave low selectivities and were less reactive The chiral oxazaborolidine catalysts have also been applied to the synthesis of complex molecules, e g the antiulcer substance cassiol and a key intermediate for the plant growth regulator gibberellic acid, which require more elaborate diene components[53 54]

The chiral oxazaborolidine **59** was also applied by Corey *et al* to the Mukaiyama-aldol and the dihydropyrone annulation reaction (hetero Diels-Alder reaction) of aldehydes with silyl enol ethers (eq 36)[56] For example, the reaction of Danishefsky diene with benzaldehyde was promoted at 78 °C in propionitrile by 20 mol% of chiral borane complexes **59** After treatment with trifluoroacetic acid the *R*-(-)-dihydropyrone **63** was formed with high enantioselectivity Transition state assembly **64** was proposed to explain the configurational relationships The model is based on attractive π-stacking interactions of the coordinated aldehyde with the indolyl-substituent similar to transition state model **62** Effective shielding of the *si* face of the carbonyl, when coordinated, leads to selective approach of nucleophiles (e g dienes) from the *re* face



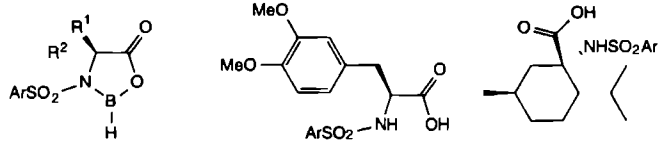
(36)

Much progress has been made in the case of chiral oxazaborolidine catalyzed asymmetric aldol reactions For example, Masamune *et al* found that the asymmetric aldol reaction of ketene silyl acetal with various aldehydes is promoted by 20 mol% of chiral oxazaborolidines **65**, derived from α,α disubstituted glycine tosylamide **66** and BH_3 THF (eq 37)[57] After acidic workup the β-hydroxy esters **67** were isolated in good yields with excellent enantioselectivity Because of the two observations that, (i) oxazaborolidines derived from *p*-toluenesulfonamides of several simple α-amino acids gave much lower yields, and (ii) the aldehyde must be added slowly in order to achieve high enantioselectivity, the authors proposed the catalytic cycle as shown below The use of a geminally disubstituted catalyst accelerates the ring closure of intermediate **68** as expected from the Thorpe Ingold effect, and the slow addition of the aldehyde reduces the accumulation of **68** which might catalyze the aldol reaction with low enantioselectivity

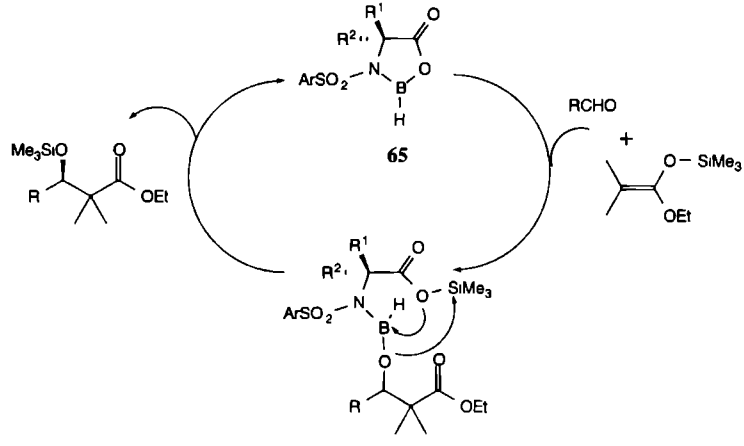


(37)

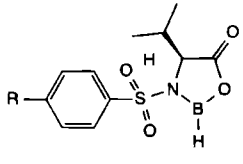
67 ee > 98%
R = *n*-Pr, $PhCH_2CH_2$



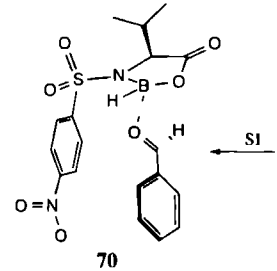
65 **66a** **66b**



Kiyooka *et al* reported that asymmetric aldol reactions of aldehydes with ketene silyl acetals (as in eq 37) in nitroethane are strongly catalyzed by 20 mol% of chiral oxazaborolidine **69a** derived from the *p*-nitrobenzenesulfonamide of (*S*)-valine and BH_3 THF[58] It was assumed that the release of the silylated product from the reaction intermediate formed with the catalyst borane complex is accelerated by nucleophilic assistance of polar solvent molecules The found enantioselectivities (*si* face attack) were explained with transition state model **70**, which is based on a AM1-optimized geometry of the chiral borane complex, apparently having a nitrogen atom with sp^2 character



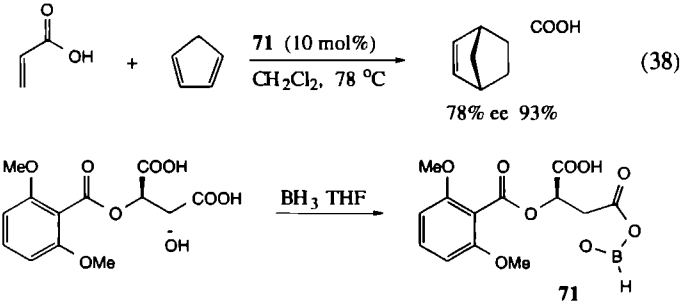
69a R = NO_2
69b R = CH_3



70

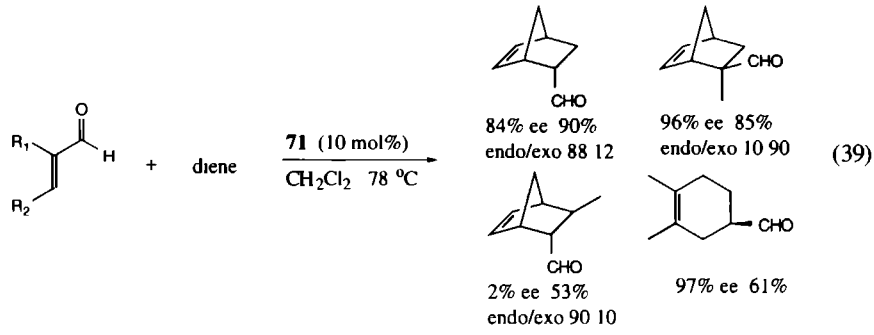
The benzaldehyde is assumed to be complexed on the lower side of the five membered ring because the upper side might be blocked by one of the methyl groups Recently the same authors reported that a stoichiometric amount of the chiral oxazaborolidine **69b** promotes the asymmetric aldol reaction of aldehydes with enol silyl ethers Subsequent asymmetric reduction in one pot affords *syn*-diols with high diastereo- and enantioselectivity[59] Again, *si* face attack of the enol silyl ethers to the aldehydes was observed, similar to **70**

Another promising chiral boron catalyst (**71**), derived from monoacylated tartaric acid and BH_3-THF, was developed by H Yamamoto *et al* It appeared to be an excellent catalyst for the asymmetric Diels-Alder reaction of cyclopentadiene and acrylic acid (eq 38)[60]



(38)

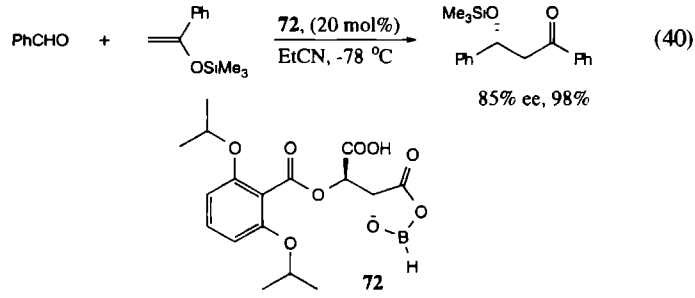
The chiral (acyloxy)borane (CAB) catalyst **71** was also shown to be an effective catalyst for the asymmetric Diels Alder reaction of unsaturated aldehydes (eq 39)[61] Some striking features of the process are the α-substituent on the dienophile increases the enantioselectivity (acrolein vs methacrolein), whereas β-substitution dramatically decreases it (crotonaldehyde) In the case of substrates having substituents at both α- and β-positions, high enantioselectivity was observed The CAB catalyst **71** is also effective in an intramolecular Diels Alder reaction of 2-methyl-(*E*,*E*)-2,7,9-decatrienal which proceeds with high diastereo- and enantioselectivity[62]



(39)

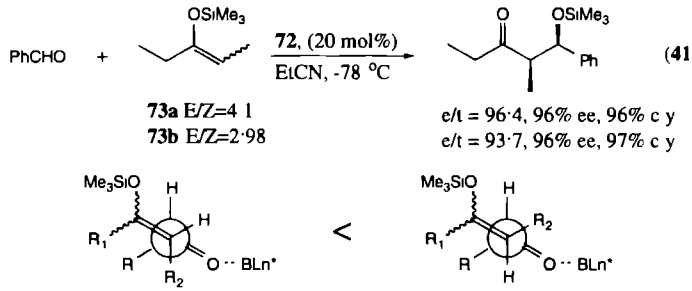
The chiral (acyloxy)borane (CAB) complex **72** (20 mol%) was shown to be an excellent catalyst for the Mukaiyama condensation of simple enol silyl ethers of ketones with various aldehydes in propionitrile at -78 °C (eq 40)[63] The products were formed in a highly diastereo- and enantioselective manner (up to 96% ee) under mild reaction conditions Predominant *re*-face attack

of enol ethers at the aldehyde carbonyl carbon was found in those cases where a natural tartaric acid derivative was used as the Lewis acid ligand.



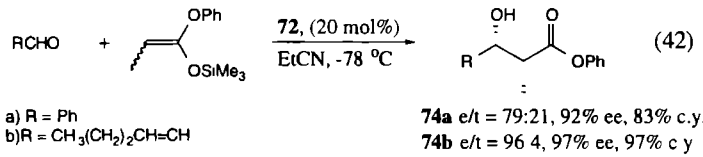
(40)

It is noteworthy that regardless of the stereochemistry of the starting silyl enol ethers **73**, generated from diethyl ketone, *erythro*-aldols were obtained with high selectivity (eq. 41). An acyclic transition state mechanism was postulated for these reactions.



(41)

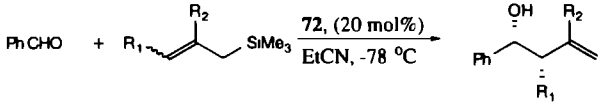
A catalytic asymmetric aldol-type reaction of ketene silyl actetals with aldehydes also proceeded smoothly with the CAB catalyst **72** to furnish *erythro* β-hydroxy esters with high enantiomeric purities (eq. 42)[64]. The sensitivity of this reaction to the substituents of the starting ketene acetals is remarkable. The reactions of ketene silyl acetals derived from ethyl or benzyl esters gave equivalent amounts of *erythro* and *threo* isomers with moderate enantioselectivities. Undesirable secondary interactions between the alkyl group and the Lewis acid were assumed to be responsible for the results. In sharp contrast, the use of phenyl ester derived ketene acetals led to good diastereo- and enantioselectivities and in high chemical yields.



(42)

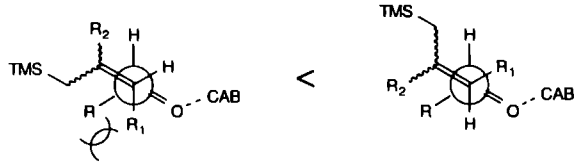
The CAB complex **72** (20 mol%) has also a powerful activity for the Sakurai-Hosomi allylation reaction of allyltrimethylsilanes with aldehydes. The *eryrtho* homoallylic alcohols **75** were obtained in modest to good yields (eq. 43)[65]. γ-Alkylated allylsilanes exhibited excellent diastereo- and enantioselectivities, affording homoallylic alcohols with a higher enantiomeric purity. Propionitrile was found to be an appropiate choice of solvent. In dichloromethane the enantio- and

diastereoselectivities dropped to e/t = 80:20 and 57% ee for **75c**. The *erythro* selectivity was independent of the geometry of the starting allylsilanes and was explained with a transition state model similar to that proposed for the *erythro* selective addition of enol silyl ethers.

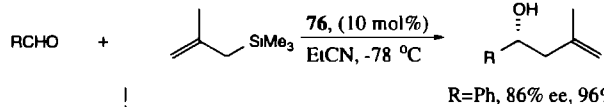


(43)

a) R_1=R_2=H — **75a** 55% ee, 46%
b) R_1=R_2=Me — **75b** 90% ee, 63%, e/t = 96:4
c) R_1=Me, R_2=Et — **75c** 96% ee, 74%, e/t = 97 3

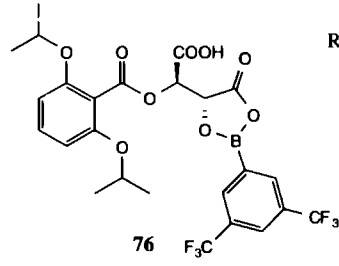


The boron substituent of CAB was found to have a strong influence on the chemical yield and the ee of the allylation adduct. The Lewis acidity of CAB **72** was improved with arylboronic acid derived catalysts. With 10 mol% CAB catalyst **76**, derived from a tartaric acid derivative and 3,5-bis(trifluoromethyl)phenylboronic acid in propionitrile, the reactivity was improved without reduction of the enantioselectivity (eq. 44)[66]. The additional advantage of boron-alkylated catalysts of type **76** is that they are stable and not as air- and moisture-sensitive as the previous catalyst **72**.



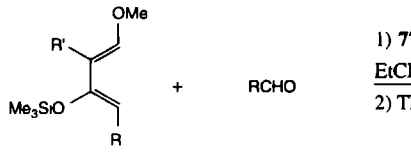
(44)

R=Ph, 86% ee, 96%
R=PhCH=CH, 85% ee, 95%



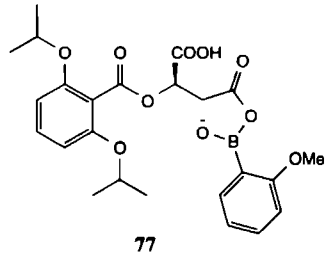
76

The hetero Diels-Alder reaction of aldehydes with Danishefsky dienes is also promoted by CAB catalysts (20 mol%) and produces dihydropyrone derivatives of high optical purities (eq.45)[67]. The efficiency of the catalyst for this type of reaction was found to be the best for CAB catalyst **77** derived from *o*-methoxyphenylboronic acid. Transition state assembly **78**, based on attractive π-stacking interactions of the coordinated aldehyde with the 2,6-diisopropoxybenzene ring, was proposed to explain the configurational relationships[67b]. Effective shielding of the *si* face of the carbonyl leads to selective approach of nucleophiles (e.g. dienes) from the *re* face. The transition state model **78** agrees well with the results of the CAB catalyzed asymmetric Diels-Alder, aldol and Sakurai-Hosomi reactions.

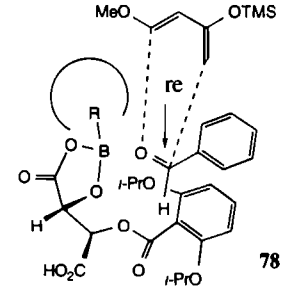


(45)

R=Ph, R=H 79% ee, 80%
R=PhCH=CH, R=Me 97% ee, 86%

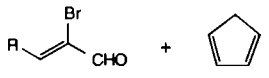


77



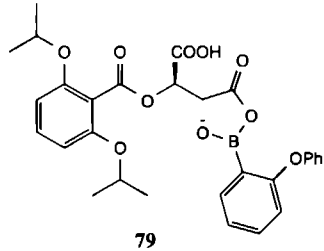
78

Yamamoto *et al* found that the enantioselective Diels-Alder reaction of α-bromo α,β-enals with dienes was also efficiently catalyzed by CAB catalyst **72** and its boron-alkylated derivatives (eq 46)[68] Highest enantioselectivity and yield (98% ee, 100%) was obtained with 10 mol% chiral catalyst **79** derived from (*o*-phenoxyphenyl)boric acid in the reaction of cyclopentadiene with α-bromoacrolein in propionitrile In dichloromethane as solvent the CAB catalyst **72** with a hydrogen-substituted boron gave highest enantioselectivities with other dienes Mechanistic studies of the CAB-catalyzed asymmetric Diels-Alder reactions of α,β-enals by NMR NOE-experiments revealed that the preferred conformation of methacrolein when complexed to CAB catalyst **72** is the *s-trans* conformation[69] Transition state assembly **80** (analog to **78**) was then proposed to explain the configurational relationships found with asymmetric Diels-Alder reactions of α,β-enals Effective shielding of the *si* face of the CAB-coordinated α,β-enal arises from π-stacking of the 2,6-diisopropoxybenzene ring and the coordinated aldehyde.

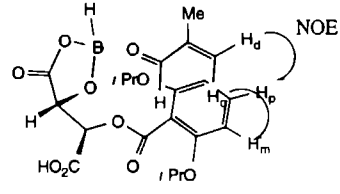


(46)

72 R=H, 95% ee, 100%
79 R=H, 98% ee, 100%
72 R=Me, 98% ee, 100%



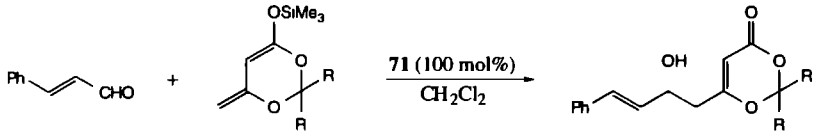
79



80

Recently, the tryptophane-derived oxazaborolidine **58** and the tartaric acid-derived (acyloxy)borane complexes **71** and **72** were tested by Sato *et al* as chiral catalysts in the asymmetric aldol reaction of 4-trimethylsiloxy-6-methylene-1,3-dioxines towards the synthesis of enantiomerically pure

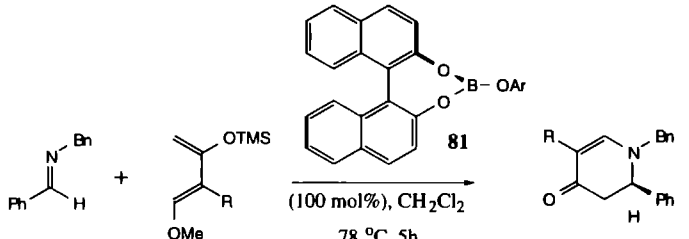
natural product goniothalamin (eq 47)[70] The highest enantioselectivity (up to 76% ee) was obtained with CAB catalyst **71** (100 mol%) in dichloromethane at -98 °C In propionitrile the enantioselectivity was lower The enantioselectivity, i e *re* face attack, was explained with a transition state assembly similar to **78** and **80**



(47)

R=Me 78 °C 73% ee
R= $(CH_2)_4$ 98 °C 76% ee

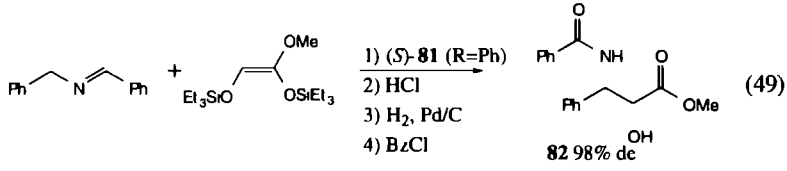
Catalytic asymmetric reactions involving imines have never received a particular interest However, Yamamoto *et al* reported an asymmetric aza-Diels-Alder reaction of aldimines with Danishefsky dienes catalyzed by a chiral boron reagent **81** (100 mol%), prepared from(*R*)-binaphtol and a triarylborate (eq 48)[71] The choice of the solvent is crucial for obtaining high optical yields, i e dichloromethane (up to 90% ee) was strikingly more effective than tetrahydrofuran or propionitrile (≈ 20% ee) This approach was applied to the synthesis of the piperidine alkaloids *S*-(-)-anabasine and *S* (+)-coniine The use of chiral imines and the chiral boron reagent **81** (Ar = Ph) led to double stereodifferentiating reactions with diastereoselectivities up to 99% de[72]



(48)

Ar=Ph R=H 82% ee 75%
Ar=3,5 xylyl, R=Me 87% ee, 66%

Despite its potential versatility in natural product synthesis very few reports of catalytic asymmetric aldol-type reactions with imines are known in the literature Recently, Yamamoto *et al* [73] reported the application of a double stereodifferentiating aldol-type reaction of chiral imines with trimethylsilyl ketene acetals catalyzed by 1 equivalent of chiral boron complex **81** (R=Ph) to provide the corresponding β-amino esters This methodology was then applied to the stereoselective synthesis of α-hydroxy-β-amino ester units involving norstatine and the taxol side chain **82** (eq 49)[73]

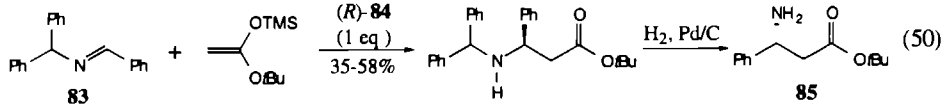


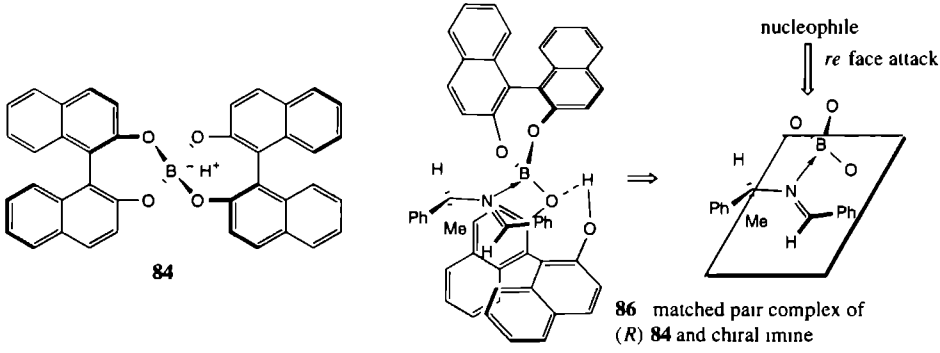
(49)

82 98% de

Interestingly, excellent enantioselectivities (> 95% ee) were obtained in the reaction of a ketene silyl acetal with various aromatic aldehyde-derived achiral N-benzhydrylimines **83** catalyzed by the Brønsted acid assisted chiral Lewis acid (BLA) **84** (eq 50)[74] The catalyst was prepared *in situ* by

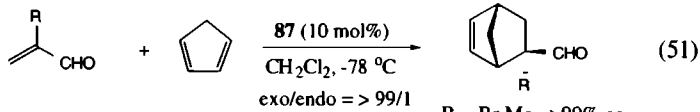
mixing a 1 2 molar ratio of triphenyl borate and optically pure binaphtol Removal of the N-benzhydryl protecting group by catalytic hydrogenation gave access to β-aryl-β-amino acids **85** in enantiomerically pure form This method was recently applied to the total synthesis of the spermidine alkaloid (*S*)-(+)-dihydroperiphylline[75] The conformations of the BLA-(chiral) imine complexes in solution were studied by NMR and X-ray The absolute configuration of the adducts can be understood in terms of a rational model (**86**) involving intramolecular hydrogen bonding via a Brønsted acid This interaction would increase the Lewis acidity of the boron and the π-basicity of the naphtoxy moiety and effectively block the *si* face of the (*E*)-imine moiety so that the nucleophile would approach the *re* face





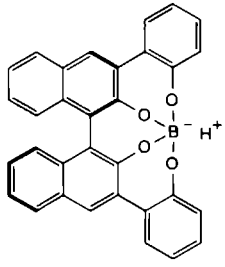
86 matched pair complex of (*R*) **84** and chiral imine

A similar Brønsted acid-assisted chiral Lewis acid catalyst **87** was designed by Yamamoto for the asymmetric Diels-Alder reaction of various α,β-enals with dienes (eq 51)[76] Using 10 mol% of catalyst, the resulting cycloadducts were obtained in quantitative yields (> 99%) with extremely high diastereo- and enantioselectivities (>99% ee)

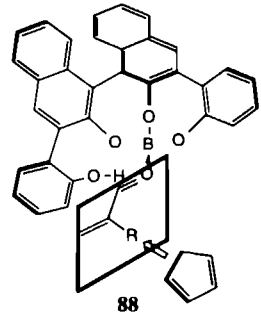


The high enantioselectivity is achieved by a double effect of intramolecular hydrogen bonding and attractive π-π donor-acceptor interaction in the transition state exerted by a phenolic group The absolute stereopreference of the Diels-Alder reactions was rationalized by transition state assembly **88** in which an attractive donor-acceptor interaction favors coordination of the dienophile at the face of the boron which is *cis* to the 2-hydroxyphenyl substituent Interestingly, a high *s-trans* preference for the conformation of the α,β-enal was assumed in contrast to the chiral oxazaborolidine system developed by Helmchen and Corey which appears to function *via* an *s-cis* α,β-enal complex Coordination of a proton of the 2-hydroxyphenyl group to an oxygen of the adjacent B-O bond in complex **88** plays an important role in the asymmetric induction Protection

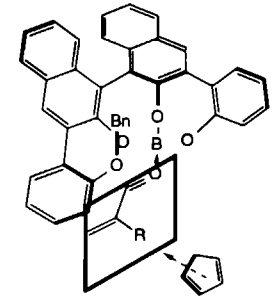
of this hydroxy functionality with a benzyl group, as in **89**, gave rise to a reversal of enantioselectivity in the reaction with methacrolein (R=Me) from 99% ee of (*R*)-isomer to 65% ee of the (*S*)-enantiomer (*exo*/*endo*=97/3) These dramatically opposite results provide evidence for the occurrence of transition state assemblies **88** and **89**



87



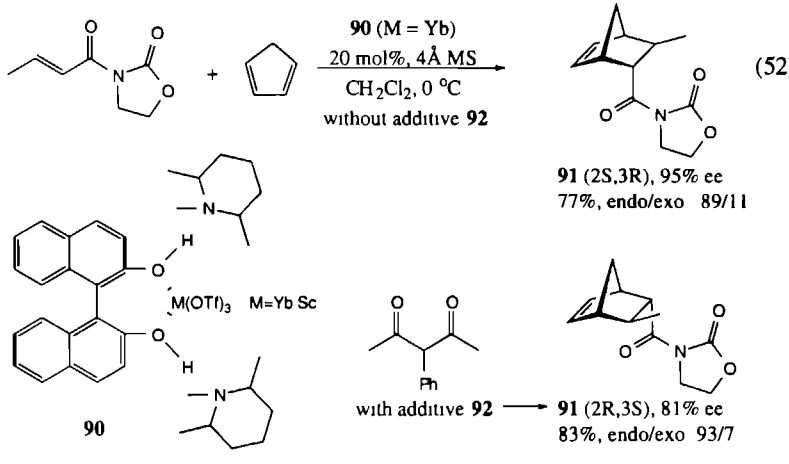
88



89

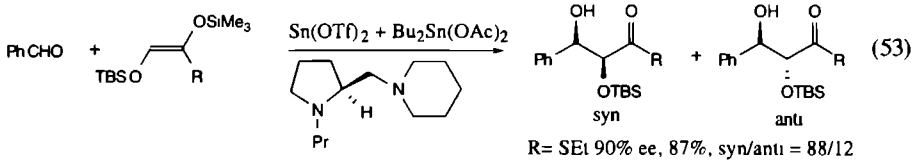
1.4.4 Other Chiral Lewis Acids

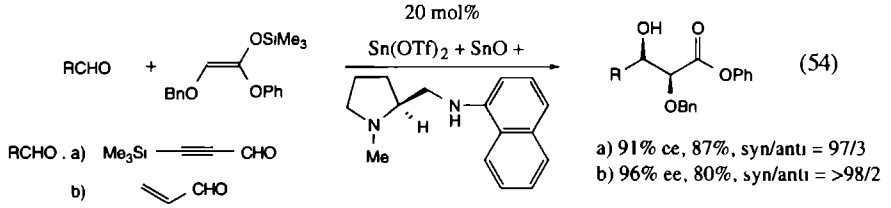
The chiral Lewis acids employed in asymmetric syntheses are generally based on traditional acids such as aluminium, titanium and boron reagents and they are well modified to realize high enantioselectivities Although lanthanide compounds were expected to act as Lewis acid reagents, only a few asymmetric reactions catalyzed by chiral lanthanide Lewis acids have been reported Danishefsky's pioneering work demonstrated that Eu(hfc)$_3$ catalyzes hetero-Diels-Alder reactions of aldehydes with siloxydienes, but the enantiomeric excesses were moderate[77] Recently, Kobayashi *et al* applied chiral lanthanide(III) triflates **90** for the asymmetric Diels-Alder reaction between acyl 1,3-oxazolidin-2-ones and cyclopentadiene (eq 52)[78] The catalysts were prepared from ytterbium or scandium trifluoromethanesulfonates, (*R*)-(+)-binaphtol and a tertiary amine The structure is characterized by the fact that hydrogen bonding occurs between the phenolic hydrogens of the binaphtol moiety and the nitrogens of the tertiary amines



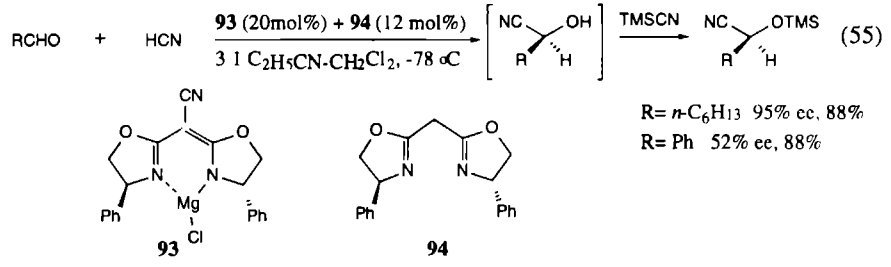
(52)

With a properly chosen tertiary amine the cycloadducts were produced with high enantioselectivity. Remarkably, the enantiofacial selectivity is controlled by additives such as phenylacetylacetone **92**. Thus, both enantiomers of the cycloadduct **91** can be prepared from a single chiral source depending on the presence or absence of appropriate achiral ligands. Kobayashi *et al.* also developed various chiral diamine-coordinated tin(II) triflates as chiral Lewis acid catalyst in asymmetric aldol and related reactions (eqs. 53 and 54)[80]. The stereo- and enantioselective preparation of *syn*- and *anti*-diol units is controlled by the ketene acetal substituents[81] or by the chiral ligands[80d,82]. This methodology was applied to the enantioselective synthesis of D-*erythro*-sphingosine and phytosphingosine (eq. 54)[83], important inhibitors of proteine kinase C and were used as such in the study of signal-transduction pathways.





Chiral bisoxazoline iron(III)[84] or magnesium[85] Lewis acids were applied by Corey *et al.* to catalyze enantioselective Diels-Alder reactions between bidentate dienophiles and cyclopentadiene Recently, a catalytic system for enantioselective cyanohydrin formation was developed based on the bisoxazoline chemistry. It involves a pair of synergistic chiral reagents **93** and **94**. Reagent **93** activates the aldehyde by complexation to magnesium and reagent **94** provides an equivalent of 'chiral cyanide ion' by activation of hydrogen cyanide (eq. 55)[86].



There are only few examples of chiral zinc complexes[87] or chiral transition state metal complexes[4a,4c] containing iron, cobalt, vanadium, nickel or chiral metallocene catalysts, (e.g. chiral zirconium catalyst[88]) that have been applied to asymmetric Diels-Alder reactions. In general, the enantioselectivities were low to moderate.

1.5 Conclusions

Until the end of 1990 the design and development of chiral Lewis acid catalysts for asymmetric synthesis have been mainly focussed on the Diels-Alder reaction of simple α,β-enals with simple dienes, e g cyclopentadiene During the course of the research described in this thesis, from the beginning of 1991 until the end of 1994, the development of asymmetric catalysis by chiral metal complexes for non-biogenetic-type reactions, and carbon-carbon bond formations in particular, has reached a level which rivals the biological approach Rationally designed catalysts ('chemzymes") can catalyze certain reactions very much in the same way as natural enzyme do in biological reactions Significant advances have been made concerning substrate-catalyst interactions and chiral recognition of substrate structures The selection of an appropriate metal center and the molecular designing of the chiral ligands are of crucial importance

Some general remarks and conclusions on the trends in asymmetric catalysis, using chiral Lewis acids, can be drawn which may be important for future design of chiral Lewis acid catalysts

1) Chiral titanium and chiral boron reagents with metallacyclic structures have received most attention Extremely high enantioselectivities in various asymmetric (cyclo)addition reactions, e g Diels-Alder, aldol, ene, and allylation reactions have been realized
2) Various chiral ligands can be applied succesfully, of which C_2-symmetric derivatives of BINOL or tartaric acid are most widely used Chiral (acyloxy)borane complexes derived from monoacylated tartaric acid or sulfonamides of α-amino acids are excellent and broadly applicable chiral Lewis acid catalysts
3) Besides classical steric hindrance (repulsive non-bonded interactions), the phenomenon of secondary attractive (π-π) interactions between chiral ligand and substrate is more and more used as a tool to obtain high enantioselectivity
4) X-ray, NMR, and modelling studies on chiral catalyst or substrate structure are increasingly being used to rationalize the observed enantioselectivities by transition state models
5) Prochiral substrates studied so far, generally contain a carbonyl group which is essential for complexation by the Lewis acid The application of chiral Lewis acid catalysts in asymmetric reactions with other than carbonyl-containing substrates, e g imines or nitrones, has been hardly investigated For example, the asymmetric 1,3-dipolar cycloaddition of nitrones is a key reaction in the synthesis of various biologically active compounds The design of chiral Lewis acid catalysts for these reactions is a challenging goal
6) Although the solvent often dramatically effects the enantioselectivity of various reactions, which effect is probably related to association-dissociation phenomena of the chiral catalyst, poor attention has been paid to the nature of such solvent effects
7) In general, Lewis acid-promoted reactions must be carried out under strictly anhydrous conditions because of the sensitivity of Lewis acid catalysts to water Alkyl- or arylated chiral (acyloxy)borane catalysts[67,68] were reported to be air and moisture-stable as were some rare earth metal triflates[78e]

8) The need for practical use and reusability of the chiral catalyst on an industrial scale will stimulate the search for effective polymer-supported chiral Lewis acid catalysts Very recently, polymer-supported chiral borane catalysts have been reported for asymmetric Diels-Alder[89a] and aldol[89b] reactions

1.6 Outline of this thesis

Chapter 1 gives a literature survey of the most important recent contributions to the application of chiral Lewis acid catalysts in asymmetric carbon-carbon bond forming reactions, the Diels-Alder reaction in particular Chapter 2 describes the chiral oxazaborolidine catalyzed Diels Alder reaction of cyclopentadiene with methacrolein and 2 bromoacrolein The effects of the side-chain substituent in the chiral amino acid ligand and of the solvent on the enantioselectivity are examined[90] Chapter 3 describes the first example of a chiral Lewis acid catalyzed 1,3-dipolar cycloaddition, i e the chiral oxazaborolidine catalyzed cycloaddition reaction of nitrones with ketene acetals[91] In chapter 4 the effects of the side-chain substituent in the catalyst, the catalyst preparation and the solvent on the enantioselectivity of the 1,3-dipolar cycloaddition are examined and optimized[92] Chapter 5 describes the chiral oxazaborolidine catalyzed cycloaddition reaction of nitrones with vinyl ethers Chapter 6 presents a short catalytic route to the asymmetric synthesis of β amino esters based on chiral oxazaborolidine catalyzed 1,3-dipolar cycloadditions Chapter 7 describes attempts to accomplish the (chiral) Lewis acid catalyzed Diels-Alder reaction between 2-cyclohexenones and functionalized dienes as a possible route to eudesmane sesquiterpenes

1.7 References and notes

1 Brown, C Ed , *Chirality in Drug Design and Synthesis*, Academic Press, New York, **1990**, Seri-Levy, A , Richards, W G *Tetrahedron Asymmetry* **1993**, *4*, 1917, for selected discussions, primarily on asymmetric synthesis in drug development, see Crossley, R *Tetrahedron* **1992**, *48*, 8155, Nugent, W A , RajanBabu, T V , Burk, M J *Science* **1993**, *259*, 479, Amato, I *Science* **1992**, *256*, 964

2 Saucy, G , Cohen, N in *Asymmetric Reactions and Processes in Chemistry*, Eliel, E L , Otsuka, S Eds , Chapter 10, *Asymmetric Reactions A Challenge to the Industrial Chemist* **1982**, ACS, Washington, 155-168 For recent review on application of asymmetric synthesis in industrial processes Kotha, S *Tetrahedron* **1994**, *50*, 3639-3662 and references cited therein

3 a) Morrison, J D Ed , *Asymmetric Synthesis*, Academic Press, New York, **1985**, Vol 1 5, b) Coppola, G M , Schuster, H F *Asymmetric Synthesis, construction of chiral molecules using amino acids*, **1987**, John Wiley & Sons, New York, c) Nogradi, M *Stereoselective Synthesis*, VCH, New York, **1989**, d) Brown, J Ed *Catalytic Asymmetric Synthesis*, *Tetrahedron Asymmetry*, **1991**, *2*, 481, e) Aitken, R A , Kilényi, S N , Eds *Asymmetric Synthesis*, **1992** Blackie Academic& Professional, Londen, f) Soai, K , Niwa, S *Chem Rev* **1992**, *92*, 833, g) Sawamura, M , Ito, Y *Chem Rev* **1992**, *92*, 857, h) Blaser, H -U *Chem Rev* **1992**, *92*, 935,

i) Davis, F A , Chen, B -C *Chem Rev* **1992**, *92*, 919, j) Rosini, C , Franzini, L , Raffaelli, A , Salvadori, P *Synthesis* **1992**, 503, k) Fuji, K *Chem Rev* **1993**, *93*, 2037-2066, l) Kunz, H , Ruck, K *Angew Chem* **1993**, *105*, 355, m) Dunina, V V , Beletskaya, I P *J Org Chem USSR* (translation) **1993**, 1913, n) Ojima, I , Ed , *Catalytic Asymmetric Synthesis*, VCH Weinheim, **1993**, o) Waldmann, H *Synthesis*, **1994**, 535, p) Noyori, R *Tetrahedron*, **1994**, *50*, 4259, q) Togni, A , Nenzanzi, L M *Angew Chem* **1994**, *106*, 517, r) Wallbaum, S , Martens, J *Tetrahedron Asymmetry* **1992**, *3*, 1475, s) Kabalka, G W , Marks, R C *J Organomet Chem* **1993**, *457*, 1-40, t) Pindur, U , Lutz, G , Otto, C *Chem Rev* **1993**, *93*, 741, u) Cole, D C *Tetrahedron* **1994**, *50*, 9517

4 For recent review on asymmetric reactions catalyzed by chiral Lewis acids, see a) Narasaka, K *Synthesis* **1991**, 1, b) Tomioka, K *Synthesis* **1990**, 541, c) Kagan, H B , Riant, O *Chem Rev* **1992**, 1007, d) Lohray, B B , Bhushan, V *Angew Chem* **1992**, *104*, 740, e) Mikami, K , Terada, M , Narisawa, S , Nakai, T *Synlett* **1992**, 255, f) Deloux, L , Srebnik, M *Chem Rev* **1993**, *93*, 763-784, g) Maruoka, K , Yamamoto, H in "Catalytic Asymmetric Synthesis" , Ojima, I , Ed , VCH Weinheim, **1993**, Chapter 9, p 413-440

5 a) Hashimoto, S -I , Komeshima, N , Koga, K *J Chem Soc , Chem Commun* **1979**, 437, b) Takemura, H , Komeshima, N , Takahashi, I , Hashimoto, S , Ikota, N , Tomioka, K , Koga, K *Tetrahedron Lett* **1987**, *28*, 5687

6 Northcott, C J , Valenta, Z *Can J Chem* **1987**, *65*, 1917

7 Chapuis, C , Jurczak, J *Helv Chim Acta* **1987**, *70*, 436

8 Maruoka, K , Itoh, T , Yamamoto, H *J Am Chem Soc* **1985**, *107*, 4573, Maruoka, K , Itoh, T , Sakurai, M , Nonoshita, K , Yamamoto, H *J Am Chem Soc* **1988**, *110*, 3588

9 Maruoka, K , Hoshino, Y , Shirasaka, T , Yamamoto, H *Tetrahedron Lett* **1988**, *29*, 3967

10 Maruoka, K , Banno, H , Yamamoto, H *J Am Chem Soc* **1990**, *112*, 7791, Maruoka, K , Banno, H , Yamamoto, H *Tetrahedron Asymmetry* **1991**, *2*, 647

11 Maruoka, K , Concepcion, A B , Yamamoto, H *Bull Chem Soc Jpn* **1992**, *65*, 3501

12 a) Corey, E J , Imwinkelried, R , Pikul, S , Xiang, Y B *J Am Chem Soc* **1989**, *29*, 3967, b) Corey, E J , Imai, N , Pikul, S *Tetrahedron Lett* **1991**, *32*, 7517, c) Corey, E J , Sarshar, S , Bordner, J *J Am Chem Soc* **1992**, *114*, 7938

13 Rebiere, F , Riant, O , Kagan, H B *Tetrahedron Asymmetry* **1990**, *1*, 199

14 Ketter, A , Glahsl, G , Herrmann, R *J Chem Res (S)* **1990**, 278, *(M)* 2118-56

15 Bao, J , Wulff, W D , Rheingold, A L *J Am Chem Soc* **1993**, *115*, 3814

16 a) Narasaka, K , Inoue, M , Okada, N *Chem Lett* **1986**, 1109, b) Seebach, D , Beck, A K , Imwinkelried, R , Roggo, S , Wonnacott, A *Helv Chim Acta* **1987**, *70*, 954, c) ref 7

17 Reetz, M T , Kyung, S -H , Bolm, C , Zierke, T *Chem Ind* **1986**, 824

18 a) Narasaka, K , Inoue, M , Yamada, T , Sugimori, J , Iwasawa, N *Chem Lett* **1987** 2409, b) Narasaka, K , Iwasawa, N , Inoue, M , Yamada, T , Nakashima, M , Sugimori, J *J Am Chem Soc* **1989**, *111*, 5340

19 a) Narasaka, K , Tanaka, H , Kanai, F *Bull Chem Soc Jpn* **1991**, *64*, 387, b) Narasaka, K , Saitou, M , Iwasawa, N *Tetrahedron Asymmetry* **1991**, *2*, 1305, c) Hayashi, Y , Narasaka, K *Chem Lett* **1989**, 793, Ichikawa, Y , Narita, A , Shiozawa, A , Hayashi, Y , Narasaka, K *J Chem Soc Chem Commun* **1989**, 1919, d) Narasaka, K , Hayashi, Y , Shimada, S *Chem Lett* **1988**, 1609, e) Narasaka, K , Yamada, T , Minamikawa, H *Chem Lett* **1987**, 2073,

Minamikawa, H , Hayakawa, S , Yamada, T , Iwasawa, N , Narasaka, K *Bull Chem Soc Jpn* **1988**, *61*, 4379, f) Narasaka, K , Kanai, F , Okudo, M , Miyoshi, N *Chem Lett* **1989**, 1187

20 Corey, E J , Matsumura, Y *Tetrahedron Lett* **1991**, *32*, 6289

21 Seebach, D , Behrendt, L , Felix, D *Angew Chem , Int Ed Engl* **1991**, *30*, 1008, Schmidt, B , Seebach, D *Angew Chem , Int Ed Engl* **1991**, *30*, 1321

22 Yoshioka, M, Kawakita, T , Ohno, M *Tetrahedron Lett* **1989**, *30*, 1657, Yoshioka, H , Kawakita, T , Yoshioka, M , Kobayashi, S , Ohno, M *Tetrahedron Lett* **1989**, *30*, 7095

23 Wada, E , Yasuoka, H , Kanemasa, S *Chem Lett* **1994**, 1637

24 a) Engler, T A , Letavic, M A , Lynch, Jr , K O , Takusagawa, F *J Org Chem* **1994**, *59*, 1179, b) Engler, T A , Letavic, M A , Reddy, J P *J Am Chem Soc* **1991**, *113*, 5068

25 a) Mikami, K , Terada, M , Motoyama, Y , Nakai, T *Tetrahedron Asymmetry* **1991**, *2*, 643, b) Terada, M , Mikami, K , Nakai, T *Tetrahedron Lett* **1991**, *32*, 935

26 a) Mikami, K , Terada, M , Nakai, T *J Am Chem Soc* **1989**, *111*, 1940, b) Mikami, K , Terada, M , Nakai, T *J Am Chem Soc* **1990**, *112*, 3949, c) Mikami, K , Narisawa, S , Shimizu, M , Terada, M *J Am Chem Soc* **1992**, *114*, 6566, d) Terada, M , Matsukawa, S , Mikami, K *J Chem Soc , Chem Commun* **1993**, 327, e) Mikami, K , Matsukawa, S *J Am Chem Soc* **1993**, *115*, 7039, f) Mikami, K , Matsukawa, S *J Am Chem Soc* **1994**, *116*, 4077, g) Mikami, K , Matsukawa, S *Tetrahedron Lett* **1994**, *35*, 3133

27 Mikami, K , Motoyama, Y , Terada, M *J Am Chem Soc* **1994**, *116*, 2812

28 Seebach, D , Beck, A K , Imwinkelried, R , Roggo, S , Wonnacott, A *Helv Chim Acta* **1987**, *70*, 954

29 Tietze, L F , Saling, P *Synlett* **1992**, 281

30 Corey, E J , Roper, T D , Ishihara, K , Sarakinos, G *Tetrahedron Lett* **1993**, *34*, 8399

31 Maruoka, K , Murase, N , Yamamoto, H *J Org Chem* **1993**, *58*, 2938

32 Keck, G E , Geraci, L S *Tetrahedron Lett* **1993**, *34*, 7827, see also Keck, G E , Krishnamurthy, D , Grier, M C *J Org Chem* **1993**, *58*, 6543

33 Kobayashi, S , Suda, S , Yamada, M , Mukaiyama, T *Chem Lett* **1994**, 97

34 Kitamoto, D , Imma, H , Nakai, T *Tetrahedron Lett* **1995**, *36*, 1861

35 Nitta, H , Yu, D , Kudo, M , Mori, A , Inoue, S *J Am Chem Soc* **1992**, *114*, 7969 For examples of autoinduction in this catalytic asymmetric reaction see Danda, H , Nishikawa, H , Otaka, K *J Org Chem* **1991**, *56*, 6740, Danda, H *Synlett* **1991**, 263

36 a) Iseki, Y , Kudo, M , Mori, A , Inoue, S *J Org Chem* **1992**, *57*, 6329, b) Ohno, H , Nitta, H , Tanaka, K , Mori, A , Inoue, S *J Org Chem* **1992**, *57*, 6778, c) Bolm, C , Muller, P *Tetrahedron Lett* **1995**, *36*, 1625

37 Kelly, T R , Whiting, A , Chandrakumar, N S *J Am Chem Soc* **1986**, *108*, 3510

38 Maruoka, K , Sakurai, M , Fujiwara, J , Yamamoto, H *Tetrahedron Lett* **1986**, *27*, 4895

39 Kaufmann, D , Bir, G *Tetrahedron Lett* **1987**, *28*, 777

40 Kaufmann, D , Boese, R *Angew Chem , Int Ed Engl* **1990**, *29*, 545

41 Hawkins, J M , Loren, S *J Am Chem Soc* **1991**, *112*, 7794

42 Hawkins, J M , Loren, S , Nambu, M *J Am Chem Soc* **1994**, *116*, 1657

43 Kobayashi, S , Murakami, M , Harada, T , Mukaiyama, T *Chem Lett* **1991**, 1341

44 Reetz, M T , Kunish, F , Heitmann, P *Tetrahedron Lett* **1986**, *27*, 4721

45 Joshi, N N , Srebnik, M , Brown, H C *Tetrahedron Lett* **1989**, *30*, 5551
46 Motoyama, Y , Mikami, K *J Chem Soc , Chem Commun* **1994**, 1563
47 Takasu, M , Yamamoto, H *Synlett* **1990**, 194
48 Sartor, D , Saffrich, J , Helmchen, G *Synlett* **1990**, 197
49 Sartor, D , Saffrich, J , Helmchen, G , Richards, C J , Lambert, H *Tetrahedron Asymmetry* **1991**, *2*, 639
50 Corey, E J , Loh, T -P *J Am Chem Soc* **1991**,*113*, 8966
51 a) Corey, E J , Loh, T -P , Roper, T D , Azimioara, M D , Noe, M C *J Am Chem Soc* **1992**, *114*, 8290, b) Corey, E J , Loh, T -P , Sarshar, S , Azimioara, M D *Tetrahedron Lett* **1992**, *33*, 6945
52 Corey, E J , Loh, T -P *Tetrahedron Lett* **1993**, *34*, 3979-3982
53 Marshall, J A , Xie, S *J Org Chem* **1992**, *57*, 2987
54 Corey, E J , Guzman-Perez, A , Loh, T -P *J Am Chem Soc* **1994**, *116*, 3611
55 Corey, E J , Cywin, C L *J Org Chem* **1992**, *57*, 7372
56 Corey, E J , Cywin, C L , Roper, T D *Tetrahedron Lett* **1992**, *33*, 6907
57 Parmee, E R , Tempkin, O , Masamune, S , Abiko, A *J Am Chem Soc* **1991**, *113*, 9365 For recent reviews on (catalytic) asymmetric Mukaiyama-aldol reactions see Sawamura, M , Ito, Y in ' Catalytic Asymmetric Synthesis" , Ojima, I , Ed , VCH Weinheim, **1993**, Chapter 7 2, p 367, Bach, T *Angew Chem* **1994**, *106*, 433
58 Kiyooka, S -i , Kaneko, Y , Kume, K *Tetrahedron Lett* **1992**, *33*, 4927
59 Kaneko, Y , Matsuo, T , Kiyooka, S -i *Tetrahedron Lett* **1994**, *35*, 4107
60 Furuta, K , Miwa, Y , Iwanaga, K , Yamamoto, H *J Am Chem Soc* **1988**, *110*, 6254
61 a) Furuta, K , Shimizu, S , Miwa, Y , Yamamoto, H *J Org Chem* **1989**, *54*, 1481, b) Furuta, K , Gao, Q , Yamamoto, H *Org Synth* **1995**, Vol 72, J Wiley & Sons, New York, pp 86-94
62 Furuta, K , Kanematsu, A , Yamamoto, H *Tetrahedron Lett* **1989**, *54*, 7231
63 Furuta, K , Maruyama, T , Yamamoto, H *J Am Chem Soc* **1991**, *113*, 1041
64 Furuta, K , Maruyama, T , Yamamoto, H *Synlett* **1991**, 439
65 Furuta, K , Mouri, M , Yamamoto, H *Synlett* **1991**, 561
66 Ishihara, K , Mouri, M , Gao, Q , Maruyama, T , Furuta, K , Yamamoto, H *J Am Chem Soc* **1993**, *115*, 11490
67 a) Gao, Q , Maruyama, T , Mouri, M , Yamamoto, H *J Org Chem* **1992**, *57*, 1951, b) Gao, Q , Ishihara, K , Maruyama, T , Mouri, M , Yamamoto, H *Tetrahedron* **1994**, *50*, 979
68 Ishihara, K , Gao, Q , Yamamoto, H *J Org Chem* **1993**, *58*, 6917
69 Ishihara, K , Gao, Q , Yamamoto, H *J Am Chem Soc* **1993**, *115*, 10412
70 Sato, M , Sunami, S , Sugita, Y , Kaneko, C *Chem Pharm Bull* **1994**, *42*, 839
71 Hattori, K , Yamamoto, H *J Org Chem* **1992**, *57*, 3264
72 a) Hattori, K , Yamamoto, H *Synlett* **1993**, 129, b) Hattori, K , Yamamoto, H *Tetrahedron* **1993**, *49*, 1749
73 a) Hattori, K , Miyata, M , Yamamoto, H *J Am Chem Soc* **1993**, *115*, 1151, b) Hattori, K , Yamamoto, H *Synlett* **1993**, 239, c) Hattori, K , Yamamoto, H *BioMed Chem Lett* **1993**, *3*, 2337, d) Hattori, K , Yamamoto, H *Tetrahedron* **1994**, *50*, 2785
74 Ishihara, K , Miyata, M , Hattori, K , Tada, T , Yamamoto, H *J Am Chem Soc* **1994**, *116*,

10520

75 Ishihara, K , Kuroki, Y , Yamamoto, H *Synlett* **1995**, 41

76 Ishihara, K , Yamamoto, H *J Am Chem Soc* **1994**, *116*, 1561

77 See for example Bednarski, N , Maring, C , Danishefsky, S *Tetrahedron Lett* **1983**, *24*, 3451, b) Bednarski, M , Danishefsky, S *J Am Chem Soc* **1986**, *108*, 7060, see also c) Quimpere, M , Jankowski, K *J Chem Soc , Chem Commun* **1987**, 676

78 a) Kobayashi, S , Ishitani, H , Hachiya, I , Araki, M *Tetrahedron* **1994**, *50*, 11623, b) Kobayashi, S , Ishitani, H *J Am Chem Soc* **1994**, *116*, 4083, c) Kobayashi, S , Ishitani, H , Hachiya, I , Araki, M *Tetrahedron Lett* **1993**, *34*, 4535, d) Kobayashi, S , Araki, M , Hachiya, I *J Org Chem* **1994**, *59*, 3758, e) For a review on lanthanide and scandium triflates as Lewis acid catalysts in organic synthesis see Kobayashi, S *Synthesis* **1994**, 689

79 Kobayashi, S , Ishitani, H , Araki, M , Hachiya, I *Tetrahedron Lett* **1994**, *35*, 6325

80 a) Mukaiyama, T , Kobayashi, S , Sano, T *Tetrahedron* **1990**, *46*, 4653, b) Kobayashi, S , Furuya, M , Ohtsubo, A , Mukaiyama, T *Tetrahedron Asymmetry* **1991**, *2*, 635, c) Kobayashi, S , Uchiro, H , Shiina, I , Mukaiyama, T *Tetrahedron* **1993**, *49*, 1761, d) Kobayashi, S , Horibe, M *J Am Chem Soc* **1994**, *116*, 9805, e) Kobayashi, S , Hayashi, T , Kawasuji, T *Tetrahedron Lett* **1994**, *35*, 9573

81 a) Mukaiyama, T , Shiina, I , Uchiro, H , Kobayashi, S *Bull Chem Soc Jpn* **1994**, *67*, 1708, b) Kobayashi, S , Kawasuji, T *Tetrahedron Lett* **1994**, *35*, 3329

82 Kobayashi, S , Hayashi, T *J Org Chem* **1995**, *60*, 1098

83 Kobayashi, S , Hayashi, T , Kawasuji, T *Tetrahedron Lett* **1994**, *35*, 9573

84 Corey, E J , Imai, N , Zhang, H -Y *J Am Chem Soc* **1991**, *113*, 728

85 Corey, E J , Ishihara, K *Tetrahedron Lett* **1992**, *33*, 6807

86 Corey, E J , Wang, Z *Tetrahedron Lett* **1993**, *34*, 4001

87 Sakane, S , Maruoka, K , Yamamoto, H *Tetrahedron* **1986**, *42*, 2203

88 Hong, Y , Kuntz, B A , Collins, S *Organometallics* **1993**, *12*, 964

89 a) Itsuno, S , Kamahori, K , Watanabe, K , Koizumi, T , Ito, K *Tetrahedron Asymmetry* **1994** *5*, 523, b) Kiyooka, S -i , Kido, Y , Kaneko, Y *Tetrahedron Lett* **1994**, *35*, 5243

90 Seerden, J -P G , Scheeren, J W *Tetrahedron Lett* **1993**, *34*, 2669

91 Seerden, J -P G , Scholte op Reimer, A W A , Scheeren, J W *Tetrahedron Lett* **1994**, *35*, 4419

92 Seerden, J -P G , Kuypers, M M M , Scheeren, J W *Tetrahedron Asymmetry* **1995**, *6*, 1441

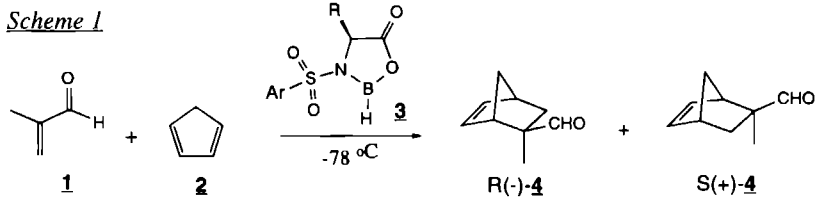
CHAPTER 2

Asymmetric Diels-Alder Reactions Catalyzed by Chiral Oxazaborolidines. Effect of the Position of an Electron Donor Functionality in the α-Side-chain Substituent on the Enantioselectivity†

2.1 Introduction

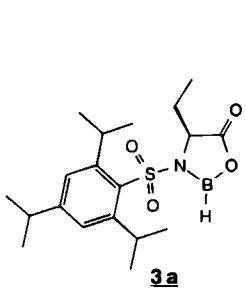
The development of chiral Lewis acids[1] that catalyze asymmetric cycloaddition reactions has been mainly focused on the asymmetric Diels-Alder reaction[2] Recently, chiral 1,3,2-oxazaborolidines **3**, simply derived from sulfonamides of α-amino acids and borane, have been used as chiral Lewis acid catalysts in the asymmetric Diels-Alder reaction of α,β–enals, e g methacrolein **1**, with simple dienes, e g cyclopentadiene **2** (*Scheme 1*)

Scheme 1

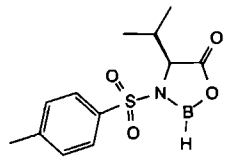


1 **2** R(-)-**4** S(+)-**4**

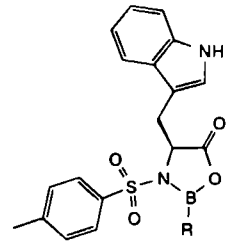
Yamamoto *et al* [3a] prepared catalyst **3a** from α-aminobutyric acid and found that the enantioselectivity of the reaction between methacrolein and 2,3-dimethylbutadiene was increased with increasing bulkiness of the benzenesulfonyl group Optical yields up to 74% ee were obtained using the 2,4,6-triisopropylbenzenesulfonamide (20 mol%) Helmchen *et al* [3b] applied the *L*-valine-derived oxazaborolidine **3b** (100 mol%) to the reaction of methacrolein with cyclopentadiene and obtained product R(-)-**4** with 64% enantioselectivity The enantioselectivity was increased to 86% ee using 60 mol% **3b** and it was shown that the presence of a donor solvent like THF was essential for high enantioselectivity[3c] Interestingly, Corey *et al* [4b] reported that for this reaction, in dichloromethane, catalyst **3e** (5 mol%), derived from (α*S*,β*R*)-β-methyltryptophan and *n*-butylboronic acid, gave complete reversal of enantioselectivity leading to S(+)-**4** with 92% ee



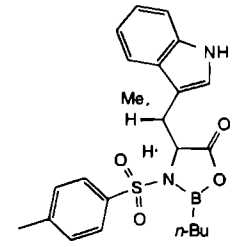
3a
Yamamoto, 1990



3b
Helmchen, 1990



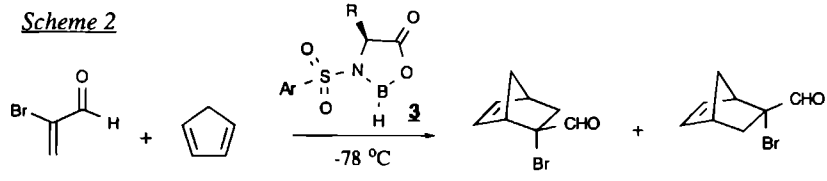
3c R = H; **3d** R = *n*-Bu
Corey, 1991



3e
Corey, 1992

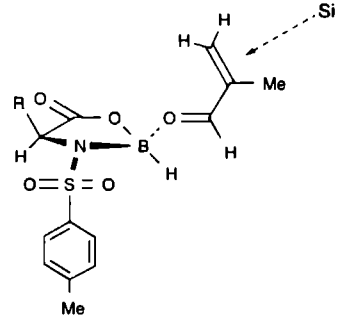
Excellent enantioselectivities (99% ee of *R*-**6**) were also observed for the **3c**-[4a], **3d**-[4a] and **3e**[4b]-catalyzed reactions of cyclopentadiene with the more reactive 2-bromoacrolein **5** which has a high preference for a *s-cis* conformation (*Scheme 2*). Replacement of β-indolylmethylene in **3e** by phenyl, cyclohexyl or isopropyl not only decreased the enantioselectivity (to about 2:1) but also changed the absolute facial preference, causing the enantiomer *S*-**6** to predominate with these catalysts[4b].

Scheme 2

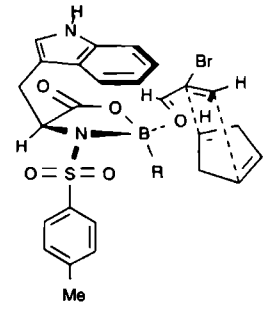


5 S-**6** R-**6**

To explain the found configurational relationships transition state model **7** was proposed by Helmchen[3c], which was mainly based on (i) steric repulsive forces between substituent R and the arylsulfonyl part of the oxazaborolidine and (ii) computational studies which suggested a *s-cis*-enal complex as preferred conformation.



7

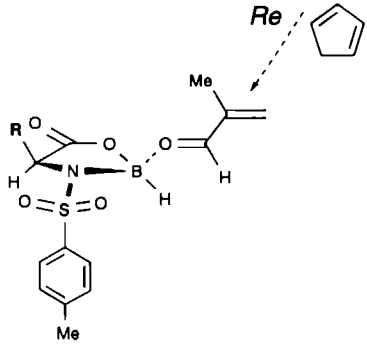


8

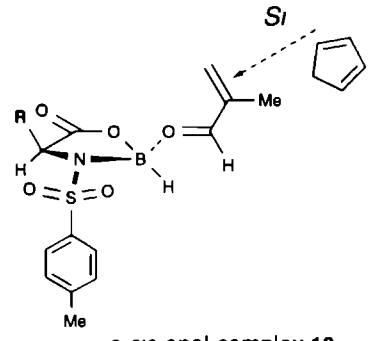
Transition state model **8** was proposed by Corey[4a,b] in which enantioselectivity is controlled by attractive donor-acceptor interactions between the indole moiety and the complexed *s-cis*-enal explaining the reversal of enantioselectivity. Until now the exact location of the functionalities for

donor-acceptor interactions is still not clear According to Corey *et al* [4b] the indole nitrogen in transition state model **8** is in proximity to the carbonyl carbon Other donor atoms of the indole ring could give a donor-acceptor interaction with the α,β-enal as well.

Even if the catalyst has a single fixed geometry in the complex with the α,β-enal the proportion of the *s-cis* and *s-trans* α,β-enal complexes must be known, since these will lead to enantiomeric products When there is no energetic preference for one of both geometries the enantioselectivity will be low, because attack from the less hindered side, i e the carboxy side of the oxazaborolidine, gives *Re*-face selectivity for *s-trans*-enal complex **9** or *Si*-face selectivity for *s-cis*-enal complex **10**

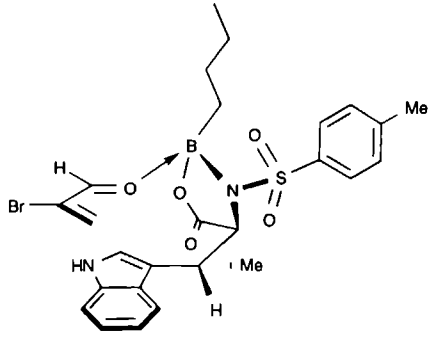


s-trans-enal complex **9**

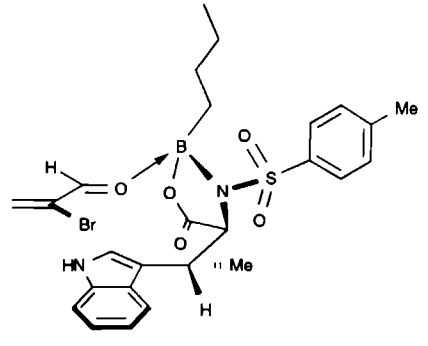


s-cis-enal complex **10**

The chiral catalyst must be properly designed to favour one geometry during complexation of the substrate Computational studies have demonstrated that the *s-cis* conformation of a Lewis acid (BF_3 OEt_2) complexed acroleine is preferred although the uncomplexed*s-trans*-enal is the preferred ground state conformation[5a]. However, very recently Corey *et al* [5b] showed by ^{1}H-NMR studies that in solution the methacrolein-BF_3 complex exists as a mixture of *s-cis* and *s-trans* geomers It was proposed that unless the chiral Lewis acid is structured to favor the *s-cis* α,β-enal complex, in solution the *s-trans* complex will predominate Transition state models **8A** and **8B** were proposed to discuss the observed enantioselectivity.



8A

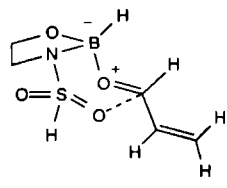


8B

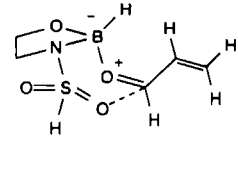
The *s-cis* complex **8A** is supposed to have much higher reactivity toward cyclopentadiene than the *s-trans* complex **8B** Addition of the diene to **8B** will result in sp^2-sp^3 transformation of the α and β

carbons and strongly increase steric repulsion between the α-bromine substituent and the indole ring Such differences also account for the enantioselectivity observed with 2-methylacrolein as reactant According to Corey *et al*, for sterically demanding side-chain substituents in the oxazaborolidine (R = isopropyl, cyclohexyl, phenyl), the *s-trans* complex is more likely involved in the transition state, as represented by model **9** However, this is in contrast to transition state model **7**, proposed by Helmchen

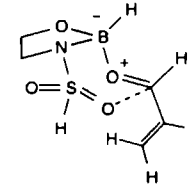
Very recently, Nevalainen investigated the properties of N-sulfonylated 1,3,2-oxazaborolidines and related α,β-enal complexes **11** in catalytic asymmetric Diels-Alder reactions by means of *ab initio* MO methods[5c]. His studies indicated that the chiral oxazaborolidine may behave as a bidentate complexation agent The oxygen of the aldehyde was found to be bound to the boron of oxazaborolidine and the carbon to one of the oxygens of the N-sulfonyl group



11a

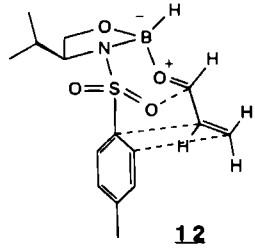


11b

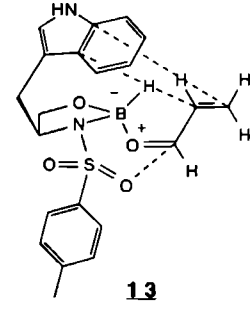


11c

The acrolein *s-trans* complexes **11a** and **11b** turned out to be more stable than the acrolein *s cis* complex **11c** On basis of these results models **12** and **13** were proposed to explain the reverse enantioselectivities found with N-tosyl-4-isopropyl- (**3b**) and N-tosyl-4-β-indolyl-methylene-1,3,2-oxazaborolidines (**3c**), respectively Both models assume that the process determining the absolute stereochemistry of the product involves π-stacking of the reacting α,β-enal and one of the aryl substituent(s) of the catalyst According to model **12**, which is based on the calculated model **11a**, the bulky aryl group, located on the opposite side of the oxazaborolidine ring system with respect to the 4-isopropyl substituent, would block one face of the vinyl moiety involved in the Diels-Alder reaction and stabilize the α,β-enal coordinated to the catalyst by intramolecular π-stacking interactions



12



13

The reversal of the absolute stereochemistry of the Diels-Alder product, which occurred when the 4-alkylsubstituent was changed into a β-indolylmethylene group, was explained by transition state model **13**, which is based on the calculated model **11b** Π-stacking interactions between the β-indolylmethylene group and the vinyl group now compete with stacking interactions between the arylsulfonyl group and this group.

These transition state models based on computational studies are rather simplified and do not account for the observed solvent effects and the steric effects of the 2-methyl or 2-bromine substituents In fact, low enantioselectivity was observed for the Diels-Alder reaction of acrolein with cyclopentadiene catalyzed by **3e**[4b] It was shown by experiment that the enantioselectivity drops dramatically if the N-tosyl group in **3e** is replaced by an oxygen atom. It was suggested that the N-tosyl group of **3c**, **3d**, and **3e** not only helps fix the position of the indole ring in the catalytic complex but also blocks the coordination of boron with the enal at the face *trans* to the indole subunit and keeps the formyl proton of the complexed α,β-enal away from the sulfonyl oxygens Assuming a catalyst-α,β-enal complex which has the molecular geometry represented by **8** with π-stacking of the indole ring and α,β-enal, the separation of the parallel π-nodal planes approximates the optimal separation of 3 3 Å The separation of these planes in model **13** is much larger and therefore it is unlikely that enantioselectivity can be explained via transition state model **13**

This chapter describes asymmetric Diels-Alder reactions catalyzed by chiral Lewis acids of type **3** The *position* of an electron donor functionality in the substituent R in **3** is varied and thereby the steric repulsion and/or electronic attractive interactions between substituents in the transition state of the reaction[6] We expected that this variation could lead to a more detailed insight in the type of donor-acceptor interactions that direct the enantioselectivity and between which groups

2.2 Results and discussion

2.2.1 Catalytic asymmetric Diels-Alder reaction of methacrolein

The reaction of cyclopentadiene with methacrolein catalyzed by new chiral oxazaborolidines **3** derived from N-(*p*-toluenesulfonyl)-*L*-α-amino acids[7] was chosen as a model reaction (*Scheme 1*) As the catalyst preparation method may influence the results, the procedures of Corey[4a] (prep method 1), as well as Yamamoto[3a] and Helmchen[3b,3c] (prep method 2) were used and studied The catalyst **3** was prepared *in situ* by adding a BH_3-THF solution (1M in THF) to a suspension of the crystalline sulfonamide in CH_2Cl_2 or THF at 0°C for 30 min (prep method 1)[3] or at room temperature for 10 min (prep method 2)[4] under a nitrogen atmosphere Freshly distilled methacrolein and cyclopentadiene (3 equivalents) were successively introduced at -78 °C After overnight reaction and usual work-up the obtained product **4** was analyzed by GC and ^{1}H-NMR The results are presented in Table 1 As can be seen in this table the two different methods of catalyst preparation do not have a significant effect on the enantioselectivity of this almost quantitative and *exo*-selective Diels-Alder reaction The table also shows that the catalyst concentration does not have a pronounced effect on the enantioselectivity[11] For R = Me, *t*-Bu, Ph, $PhCH_2$, $PhCH_2CH_2$ (entries 1a-e) the donor solvent THF gives rise to a significant increase in enantioselectivity[12] with preferential formation of *exo-R(-)*-**4** compared to the acceptor solvent CH_2Cl_2 The latter reaction mixture contains *ca* 12 eq THF originating from the catalyst preparation using 1M BH_3-THF in THF

Table 1. Enantioselective Diels-Alder reaction of methacrolein **1** and cyclopentadiene **2** catalyzed by chiral boron catalysts **3**[a] (Scheme 1)

				solvent CH_2Cl_2 (+ *ca.* 12 eq THF[10])		solvent THF		
entry	**3** : R =	prep. meth.[b]	mol% cat.[c]	exo/ endo[d]	e.e. (%)[e]	exo/ endo	e.e. (%)	abs.conf. **4**[f]
1a	Me	1	20	91/9	20	98/2	53	R(-)
1b	*i*-Bu	1 1 1	20 50 100	96/4 97/3 98/2	22 60 41	98/2	71	R(-) R(-) R(-)
1c	Ph	1 2	20 20	95/5 96/4	40 46	98/2 98/2	80 74	R(-) R(-)
1d	$PhCH_2$	1 1 2	20 60 5	95/5 95/5 94/6	6 6 6	95/5 95/5	28 30	R(-)[g] R(-) R(-)
1e	$PhCH_2CH_2$	1 2	20 20	98/2 98/2	62 58	98/2 97/3	70 72	R(-) R(-)
1f	$PhCH_2OCH_2$	1 1 2 2	20 60 20 5	96/4 94/6 94/6	44 48 56	97/3 96/4 97/3	32 33 33	S(+) S(+) S(+) S(+)
1g	*cyclo*-hexyl-CH_2OCH_2	2	20	98/2	18	98/2	22	S(+)

[a] All reactions were carried out overnight (ca 16 h) using 4 mmol of methacrolein at -78 °C, the product **4** was obtained in a quantative yield (*ca* 99%), [b] catalyst preparation according to references cited in text, [c] The chiral ligands were efficiently recovered, [d] Determined by 100 MHz ^{1}H-NMR analysis, [e] Determined by ^{1}H-NMR analysis with the chiral shift reagent Eu(hfc)$_3$, [f] For assignment of absolute configuration the product was purified by silicagel "flash"chromatography (CH_2Cl_2 cyclohexane = 3 2) and optical rotation was measured and compared with literature data[9]

Helmchen *et al.* found almost complete loss of enantioselectivity when the catalyst **3b** was prepared from 1M BH_3-SMe_2 in CH_2Cl_2. It was suggested that in acceptor solvent CH_2Cl_2 the catalyst associates *via* its carbonyl group (see Figure 1) which leads to a decrease of the enantioselectivity by shielding of the C_α-*Si* enal face, as shown in model **7**[3c]. However, in all experiments of Table 1 the catalyst was prepared from BH_3-THF (1M solution in THF) so we may assume that in our cases the oxazaborolidines are present as monomeric species. The observed increase of *Si*-face attack stimulated by excess THF may originate from a selective solvation of the α,β-enal in which the ratio of the *s-cis/s-trans* complex is influenced in favor of the *s-cis* complex. The

enantioselectivities of entries 1a, 1b and 1c can be satisfactorily explained with transition state model 7, in which substituent R only operates as a group that causes steric repulsion and leads to preferential formation of the *exo-R(-)*-enantiomer

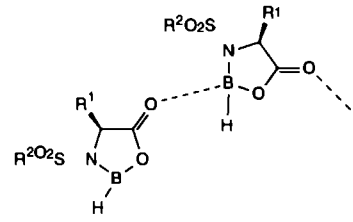
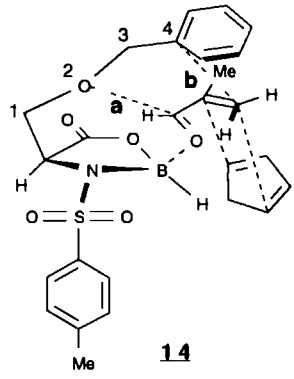


Figure 1. Self-association of oxazaborolidines

For reversal of enantioselectivity the *position* of atoms with electron donating ability is very important These donor atoms should be located at position 2 and 4 of substituent R (see transition state model **14**), as appears from the results in entries 1c to 1f This is explained in **14** for R = $PhCH_2OCH_2$ (entry 1f) A strong donor-acceptor interaction is possible between the oxygen atom at position 2 of the substituent R and the carbonyl carbon of the complexed dienophile (interaction **a**) Molecular models show that a second donor-acceptor interaction is possible between the *ipso*-carbon atom of the phenylsubstituent in position 4 and the β-carbon atom of the dienophile (interaction **b**) which forces the dienophile in the *s-cis* conformation The lower enantioselectivity found for entry 1g may be ascribed to the lack of the second donor-acceptor interaction **b** in position 4



14

No reversal of enantioselectivity was observed for R = $PhCH_2CH_2$ (entry 1e) although the position of the phenyl ring is very similar to the position of the phenyl part in the indolylmethyl substituent in **3e** which gave rise to very high enantioselectivity This indicates that a phenyl ring at position 3 is not sufficient for effective donor-acceptor interactions with the dienophile and that the phenyl ring of the indolyl group does not contribute to the donor-acceptor interactions The presence of the nitrogen atom in the indolyl group might be crucial The low enantioselectivity found for R = $PhCH_2$ (entry 1d) can be ascribed to the weak donor-acceptor interaction of the aromatic sp^2 carbon atom at position 2 of the substituent R with the dienophile, so that steric repulsion (according to model 7) and complexation (according to model **14**) are competing

2.2.2 Catalytic asymmetric Diels-Alder reaction of 2-bromoacrolein

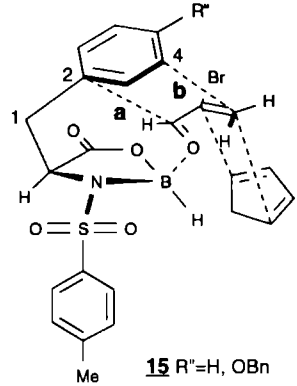
We rationalized that stronger donor-acceptor interactions between the side-chain substituent of the oxazaborolidine and the α,β-enal can be expected in the cycloaddition reaction with the more electron-poor 2-bromoacrolein **5**[4]. Therefore, we first investigated the reaction of cyclopentadiene with 2-bromoacrolein at -78 °C in CH_2Cl_2 with 5 mol% of catalyst **3** for R = Me, $PhCH_2$ and $PhCH_2OCH_2$ (*Scheme 2*). The reactions were complete within 3 hours.

Table 2. Enantioselective Diels-Alder reaction of 2-bromoacrolein **5** and cyclopentadiene **2** catalyzed by chiral boron catalysts **3** (Scheme 2)[a]

entry	**3** : R =	prep. meth.[b]	mol% cat.[c]	exo/endo[d]	e.e (%)[e]	abs conf **6**[f]
2a	Me	2	5	98/2	33	S
2b	$PhCH_2$	2	5	95/5	55	R
2c	4-MeO-$PhCH_2$	2	10	96/4	72	R
2d	4-$PhCH_2O$-$PhCH_2$	2	10	96/4	81	R
2e	$PhCH_2OCH_2$	2	5	96/4	54	R

[a] All reactions were carried out overnight (ca. 16 h) using 4 mmol of methacrolein at -78 °C, the product **6** was obtained in *ca* 99% yield, [b] See text, [c] The chiral ligands were efficiently recovered, [d] Determined by 100 MHz ^{1}H-NMR analysis, [e] Determined by ^{1}H-NMR analysis with the chiral shift reagent Eu(hfc)$_3$. [f] For assignment of absolute configuration the product was compared with literature data[4]

The results in Table 2 show that now reversal of enantioselectivity occurs for R = $PhCH_2$ (entry 2b). This can be explained by assuming that a transition state of type **15** is predominantly present



15 R"=H, OBn

We can expect that enhanced electron density in positions 2 and 4, induced by electron donating *para*-substituents on the aromatic ring, will increase the electron donor-acceptor interactions in the transition state We therefore screened commercially available O-protected *L*-tyrosine derivatives as suitable chiral precursors of the catalyst A higher enantioselectivity was indeed observed with a *para*-MeO (72% ee, entry 2c) and a *para*-$PhCH_2O$ substituent (81% ee, entry 2d) The reaction of methacrolein with cyclopentadiene catalyzed by these *L*-tyrosine-derived oxazaborolidines proceeded in a quantitative yield but still with very low enantioselectivity (ca 5% ee), as observed for *L*-phenylalanine-derived oxazaborolidine (Table 1, entry 1d) Probably, the donating *para*-substituents do not cause sufficiently strong donor-acceptor interactions with methacrolein

2.3 Conclusions

The following conclusions can be drawn from the results

1) The asymmetric Diels-Alder reaction of cyclopentadiene with α,β-enals is strongly catalyzed by a variety of chiral oxazaborolidines (5-20 mol%) at -78 °C and gives the *exo*-cycloadducts in quantitative yield,
2) The enantioselectivity of the reaction is determined by the presence, or absence, of donor atoms in the side-chain substituent,
3) For sterically demanding side-chain substituents in the oxazaborolidine the presence of the donor solvent THF, which prevents dimerization of the catalyst, enhances the enantioselectivity, in agreement with Helmchen's model **7**,
4) For *L*-serine(O benzyl ether)- and *L*-tyrosine(O-benzyl ether)-derived oxazaborolidines attractive interactions between donor atoms, in position 2 and 4 of the side-chain substituent, of the catalyst and the enal lead to reversal of enantioselectivity, as depicted in transition state models **14** and **15**,
5) The alternative transition state models **12** and **13** proposed by Nevalainen[5c], based on computational studies, are too much simplified and do not account for the observed solvent effects and the steric hindrance exerted by the 2-methyl or 2-bromine substituent of the enal Based on experimental data[4], it is unlikely that enantioselectivity can be explained via transition state model **13**
6) The use of phenylalanine- and serine-derived oxazaborolidines, having more electron-rich aromatic rings in the side-chain substituent, in Diels-Alder reactions of methacrolein are assumed to give higher enantioselectivities, probably due to stronger donor-acceptor interactions

2.4 Experimental Section

Dichloromethane was dried and distilled on CaH_2 and stored over 4Å molecular sieves Tetrahydrofuran was distilled from benzophenone ketyl All reactions were carried out under a dry nitrogen or argon atmosphere ^{1}H-NMR spectra and ^{13}C-NMR were recorded on a Varian EM 390 (90 MHz, CW), a Bruker AM-100 (100 MHz, FT) or a Bruker AM-400 (400 MHz, FT) spectrometer with TMS as an internal standard Gas chromatography was performed on a Hewlett-Packard 5710A GC-instrument equipped with a capillary HP cross-linked methyl silicone (25 m x 0 31 mm) column Enantioselectivities were determined by LIS-NMR (Lanthanide Induced Shift NMR) using (+)-Eu(hfc)$_3$ as the chiral shift reagent Optical rotations were measured on Perkin-Elmer 241 polarimeter at the sodium line Cyclopentadiene (thermally cracked from dicyclopentadiene over Cu-powder) and methacrolein were distilled before use under a dry nitrogen atmosphere 2-Bromoacrolein was prepared from acrolein according to the literature[4] The synthesis of N-tosyl α-amino acids from commercially available α-amino acids and *p*-toluenesulfonic acid chloride was done under Schotten-Baumann conditions using 1N sodium hydroxide in a water/diethyl ether mixture or in 2 5 equiv Et_3N in water/THF (10 1, v v)[4a] according to the literature[3 7]

N-*p*-Toluenesulfonyl-*L*-phenylglycine-OH m p 161-162 °C, $[\alpha]_D^{20}$= +127 6 (c = 0 8, acetone), ^{1}H-NMR ($CDCl_3$, 100 MHz) δ (ppm) 7 41 2H, d, J = 8 1 Hz, H-arom (tosyl), 7 03 7H, m, C_6H_5 and 2H-arom (tosyl), 6 74 1H, m, NH (D_2O exchange), 4 86 1H, m, PhC*H*, 4 74 1H, br s, OH (D_2O exchange), 2 07 3H, s, CH_3 (tosyl)

N-*p*-Toluenesulfonyl-*L*-homophenylalanine-OH m p 95 °C, $[\alpha]_D^{20}$= +30 8 (c = 1 5, acetone), ^{1}H-NMR ($CDCl_3$, 100 MHz) δ (ppm) 7 71 2H, d, J = 8 2 Hz, H-arom (tosyl), 7 1-7 3 8H, m, 7H-arom + OH (D_2O exchange), 5 55 1H, d, J = 8 7 Hz, NH (D_2O exchange), 3 96 1H, m, C-H, 2 63 2H, t, J = 7 8 Hz, C*H*$_2$-CH$_2$, 2 39 3H, s, CH_3 (tosyl), 2 00 2H, m, J = 7 8 Hz, CH_2-C*H*$_2$-CH

N-*p*-Toluenesulfonyl-*L*-serine(O-benzyl ether)-OH m p 110-112°C, $[\alpha]_D^{20}$= +22 2 (c = 2 5, 96% EtOH), ^{1}H NMR ($CDCl_3$, 100 MHz) δ (ppm) 7 71 2H, d, J = 8 3 Hz, H-arom (tosyl), 7 27 7H, m, C_6H_5 and 2H-arom (tosyl), 5 58 1H, m, NH (D_2O exchange), 4 47 2H, s, PhC*H*$_2$O, 4 10 1H, m, NH-C*H*-CH$_2$, 4 0 1H, br s, OH (D_2O exchange), 3 5-3 9 2H, m, CH_2O, 2 39 3H, s, CH_3

N-*p*-Toluenesulfonyl-*L*-serine(O-(2-cyclohexyl)methyl ether)-OH was prepared from *L*-serine(O-benzyl ether)-OH by hydrogenation (40 psi bar H_2) using 5% Rh/Al_2O_3 as catalyst in the solvent mixture MeOH/AcOH/H_2O (5 2 5, v/v/v) for 24 hours reaction time and subsequent reaction of the isolated derivatized α-amino acid with *p*-toluenesulphonic acid chloride under usual conditions, m p = 88 °C, $[\alpha]_D^{25}$= +27 7 (*c* = 1, $CHCl_3$), 68% overall yield ^{1}H-NMR ($CDCl_3$, 100 MHz) δ (ppm) 7 74 2H, d, J = 8 4 Hz, H-arom (tosyl), 7 30 2H, d, J = 8 2 Hz, H-arom (tosyl), 5 55 1H, d, J = 8 7 Hz, NH (D_2O exchange), 5 3 1H, br s, OH (D_2O exchange), 4 06 1H, m, NH-C*H*-

CH_2, 3 5-3 9 2H, m, CH_2O, 3 18 2H, d, J = 6 Hz, CH_2, 2 42 3H, s, CH_3 (tosyl), 0 9-1 8 11H, m, C_6H_{11}-CH_2

N-*p*-Toluenesulfonyl-*L*-tyrosine(O-methyl ether)-OH ^{1}H-NMR ($CDCl_3$, 100 MHz) δ (ppm) 9 77 1H, br s, OH (D_2O exchange), 7 46 2H, d, J = 8 3 Hz, H-arom (tosyl), 7 07 2H, d, J = 8 2 Hz, H-arom (tosyl), 6 89 2H, d, J = 8 4 Hz, H-arom , 6 62 2H, d, J = 8 4 Hz, H-arom , 5 43 1H, m, NH (D_2O exchange), 4 06 1H, m, C*H*-CH_2, 3 66 3H, s, CH_3O, 2 90 2H, m, CH_2, 2 27 3H, s, CH_3

N-*p*-Toluenesulfonyl-*L*-tyrosine(O-benzyl ether)-OH m p 132-134 °C, ^{1}H-NMR ($CDCl_3$, 100 MHz) δ (ppm) 8 30 1H, br s, OH (D_2O exchange), 7 57 2H, d, J = 8 3 Hz, H-arom (tosyl), 7 34 5H, m, C_6H_5, 7 16 2H, d, J = 8 1 Hz, H-arom (tosyl), 7 00 2H, d, J = 8 6 Hz, H-arom , 6 78 2H, d, J = 8 5 Hz, H-arom , 5 40 1H, d, J = 8 7 Hz, NH (D_2O exchange), 4 97 2H, s, CH_2O, 4 14 1H, m, NH-C*H*-CH_2, 3 13 2H, m, CH_2, 2 36 3H, s, CH_3 (tosyl)

2-Bromoacrolein (5)

Following a literature procedure[4a,14], acrolein (freshly distilled) was converted into 2-bromoacrolein in two steps by dibromination with bromine at low temperature (0 °C, 15 min) followed by dehydrobromination with triethylamine as a base The product was a colorless oil (bp 34 °C/15 mm Hg, lit [2e] 38 °C/ 22 mm Hg, lit [4a] 46-48 °C/28 mm Hg), IR (film) 1700 (C=O) cm $^{-1}$, ^{1}H-NMR ($CDCl_3$, 100 MHz) δ 6 89 1H, d, J = 3 4 Hz, C*H*H, 6 92 1H, d, J = 3 4 Hz, CH*H*, 9 26 1H, s, CHO

Chiral oxazaborolidine catalyzed asymmetric Diels-Alder reactions (General procedure)

The chiral oxazaborolidines **3** were prepared *in situ* from suspended N-tosyl-*L*-α-amino acids at room temperature, using a reaction time of 10 min (preparation method 1)[4], or at 0 °C, using a reaction time of 30 min (preparation method 2)[3] The reactions were carried out under an inert nitrogen atmosphere and the BH_3 THF (1M solution in THF) was added in equimolar amounts in dry solvent (4 ml) The clear solution was cooled to -78 °C and subsequently the freshly distilled α,β-enal **1** or **5** (4 mmol) and cyclopentadiene **2** (12 mmol) were added After 5-24 hours the reaction mixture was quenched at -78 °C with saturated aqueous bicarbonate, extracted with diethyl ether, dried with sodium sulphate and concentrated under vacuum with a rotary evaporator at room temperature The crude cycloadducts **4** or **6** were isolated and were further purified by flash chromatography on silica gel using dichloromethane cyclohexane = 3 2 (v/v) as eluent The enantioselectivity of the cycloadduct was determined by ^{1}H-NMR in the presence of *ca* 0 25-0 5 equiv of (+)-Eu(hfc)$_3$ as a chiral shift reagent The following resonances are diagnostic ^{1}H-NMR δ (ppm) 16 3 s, 2-CHO, *S*-(+)-**4**, and 16 1 s, 2-CHO, *R*-(-)-**4** The absolute configuration was determined by optical rotation and compared to literature data[9]

(*1R, 2R, 4R*)-2-Bromobicyclo[2.2.1]hept-5-ene-2-carboxaldehyde (6)[2e]

Semi-solid, TLC, R_f = 0 68 (hexane-EtOAc, 4 1, v/v), IR (film) 2980, 2830, 1725 (C=O), 1440 cm

[1], ^{1}H-NMR ($CDCl_3$, 100 MHz) δ 1 34 1H, d, J = 9 4 Hz, H-7, 1 40-1 60 2H, m, H-7, H-3, 2 65 1H, dd, J = 4 and 13 Hz, H-3, 3 0 1H, br s, H-4, 3 3 1H, br s, H-1, 6 15 1H, dd, J = 3 0 and 5 6 Hz, H-5, 6 48 1H, dd, J = 3 0 and 5 6 Hz, H-6, 9 35 (endo) and 9 56 (exo) 1H, s, CHO The enantioselectivity was determined from the ratio of the integrals of the shifted resonance signals of the aldehyde proton in the ^{1}H-NMR spectrum of the cycloadduct, which was recorded in the presence of *ca* 0 5 equiv of chiral shift reagent (+)-Eu(hfc)$_3$ The following resonances are diagnostic ^{1}H-NMR δ (ppm) 15 44 s, CHO, (*1R,2R,4R*)-**6** and 15 24 s, CHO, (*1S,2S,4S*)-**6** The absolute configuration was determined by comparison to the known compound (*1R,2R,4R*)-**6** obtained from the *L*-tryptophane-derived-oxazaborolidine catalyzed reaction[2e]

2.5 References and Notes

† Partially taken from Seerden, J -P G , Scheeren, J W *Tetrahedron Lett* **1993**, *34*, 2669-2672

1 Narasaka, K *Synthesis* **1991**, 1, Tomioka, K *Synthesis* **1990**, 541 Review on asymmetric reactions with chiral Lewis acid catalysts see Maruoka, K , Yamamoto, H in "Catalytic Asymmetric Synthesis" , Ojima, I , Ed , VCH Weinheim, **1993**, Chapter 9, p 413-440

2 See Chapter 1 For reviews see a) Kagan, H B , Riant, O *Chem Rev* **1992**, 1007, b) Lohray, B B , Bhushan, V *Angew Chem* **1992**, *104*, 740, c) Deloux, L , Srebnik, M *Chem Rev* **1993**, *93*, 763-784 Recent examples d) chiral boron reagents Maruoka, K , Murase, N , Yamamoto, H *J Org Chem* **1993**, *58*, 2938-2939, e) Ishihara, K , Gao, Q , Yamamoto, H *J Org Chem* **1993**, *58*, 6917-6919, Ishihara, K , Gao, Q , Yamamoto, H *J Am Chem Soc* **1993**, *115*, 10412-10413, f) Hawkins, J M , Loren, S , Nambu, M *J Am Chem Soc* **1994**, *116*, 1657, g) Brønsted acid-assisted chiral boron reagents Ishihara, K , Yamamoto, H *J Am Chem Soc* **1994**, *116*, 1561-1562, Ishihara, K , Miyata, M , Hattori, K , Tada, T , Yamamoto, H *J Am Chem Soc* **1994**, *116*, 10520-10524, chiral titanium reagents h) Corey, E J , Roper, T D , Ishihara, K , Sarakinos, G *Tetrahedron Lett* **1993**, *34*, 8399-8402, i) Mikami, K , Motoyama, Y , Terada, M *J Org Chem* **1994**, *116*, 2812-2820, j) Engler, T A , Letavic, M A , Lynch, Jr , K O , Takusagawa, F *J Org Chem* **1994**, *59*, 1179, chiral aluminium reagent k) Bao, J , Wulff, W D , Rheingold, A L *J Am Chem Soc* **1993**, *115*, 3814-3815, l) polymer-supported chiral boron reagent Itsuno, S , Kamahori, K , Watanabe, K , Koizumi, T , 48Ito, K *Tetrahedron Asymmetry* **1994**, *5*, 523-526, m) chiral boron reagent in hetero Diels Alder Motoyama, Y , Mikami, K *J Chem Soc Chem Commun* **1994**, 1563-1564, n) chiral lanthanide reagents Kobayashi, S , Araki, M , Hachiya, I *J Org Chem* **1994**, *59*, 3758-3759, o) Kobayashi, S , Ishitani, H , Hachiya, I , Araki, M *Tetrahedron* **1994**, *50*, 11623-11636, p) chiral bimetallic boron Lewis acid Reilly, M , Oh, T *tetrahedron Lett* **1994**, *35*, 7209-7212

3 a) Takasu, M , Yamamoto, H *Synlett* **1990**, 194, b) Sartor, D , Saffrich, J , Helmchen, G *Synlett* **1990**, 197, c) Sartor, D , Saffrich, J , Helmchen, G , Richards, C J , Lambert, H *Tetrahedron Asymmetry* **1991**, *2*, 639

4. a) Corey, E.J.; Loh, T.-P. *J. Am. Chem. Soc.* **1991**,*113*, 8966; b) Corey, E.J.; Loh, T.-P.; Roper, T D.; Azimioara, M.D.; Noe, M.C. *J. Am. Chem. Soc.* **1992**, *114*, 8290; c) Marshall, J.A.; Xie, S. *J. Org. Chem.* **1992**, *57*, 2987; d) Corey, E.J.; Loh, T.-P. *Tetrahedron Lett.* **1993**, *34*, 3979-3982; e) Corey, E.J.; Cywin, C.L. *J. Org. Chem.* **1992**, *57*, 7372.
5. a) Guner, O.F.; Ottenbrite, R.M.; Shillady, D.D.; Alston, P.V. *J. Org. Chem.* **1987**, *52*, 391-394; b) Corey, E.J.; Loh, T.-P.; Sarshar, S.; Azimioara, M. *Tetrahedron Lett.* **1992**, *33*, 6945; c) Nevalainen, V. *Tetrahedron : Asymmetry* **1994**, *5*, 767-772.
6. For the effect of a remote phenyl group in chiral dienes on the stereoselectivity of Diels-Alder reactions see: de Bie, J.F.M.; van Strijdonck, G.P.F; Seerden, J.-P.G.; Beurskens,G.; Scheeren, J.W. *Tetrahedron Lett.* **1990**, *31*, 7233; Siegel, C.; Thornton, E.R. *Tetrahedron. Asymmetry* **1991**, *2*, 1413.
7 The sulphonamides were prepared from commercially available amino acids and derivatives according to a procedure described in: Houben-Weyl, *'Methoden der Organischen Chemie'*, Band 15/1, *Synthese von Peptiden* I, 4eAuflage, Georg Thieme Verlag, Stuttgart, **1974**, pp. 223-233. Under the reaction conditions no racemisation of the sulphonamides occurs. See also: Berry, M.B.; Craig, D. *Synlett* **1992**, 41-44.
8. Complementary results (formation of *S(+)*-**4**) were obtained when instead of *L(+)*-phenylalanine (entry **1d**) the unnatural *D(-)*-phenylalanine was used as starting material for the chiral catalyst.
9. Hashimoto, S.; Komeshima, N.; Koga, K. *J. Chem. Soc. Chem. Commun.* **1979**, 437.
10. The catalyst preparation starts with BH_3-THF (1M solution in THF) and introduces ca. 12 eq. THF into the reaction mixture.
11. a) ref.3c; b) Kobayashi, S.; Fujishita, Y.; Mukaiyama, T. *Chem. Lett.* **1990**, 1455; c) Hiroi, K., Arinaga, Y.; Ogino, T. *Chem. Lett.* **1992**, 2329-2332; d) Ando, K.; Takemasa, Y.; Tomioka, K., Koga, K. *Tetrahedron* **1993**, *49*, 1579-1588.
11. Higher catalyst concentration can in principle cause association of the catalyst, but this effect will be counterbalanced by a concomitant increase of the THF concentration (ref. 10)
13. Corey, E.J.; Guzman-Perez, A.; Loh, T.-P. *J. Am. Chem. Soc.* **1994**, *116*, 3611-3612.
14. Chow, Y L.; Bakker, B.H.; *Can. J Chem.* **1982**, *60*, 2268.

CHAPTER 3

Asymmetric 1,3-Dipolar Cycloaddition Reactions of Nitrones with Ketene Acetals Catalyzed by Chiral Oxazaborolidines†

3.1 Introduction

The asymmetric 1,3-dipolar cycloaddition reaction of nitrones, followed by some functional group transformations including a reductive cleavage of the nitrogen-oxygen bond in the cycloadducts, has received much attention in the last decade and plays an important role in natural product synthesis[1] Most advances have been made with chiral nitrones and chiral dipolarophiles[2] In view of the numerous reports describing the successful stereocontrol achieved in (chiral) Lewis acid catalyzed Diels-Alder reactions[3], it can be expected that (chiral) Lewis acid catalysis will play a similar role in dipolar cycloadditions However, until very recently no successful reactions were reported A serious problem may be that 1,3-dipoles, such as nitrones, act as much stronger bases than dienes It has been assumed that these dipoles have a tendency to form inactive dipole/Lewis acid complexes

Succesful application of Lewis acid catalysis in 1,3-dipolar cycloadditions of nitrones with alkenes will be strongly determined by the alkene substituents These substituents affect the HOMO-LUMO interaction in the transition state, i e the activation energies, and consequently the reaction rates

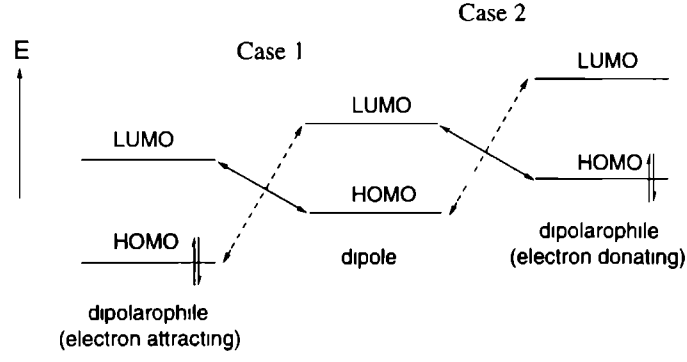


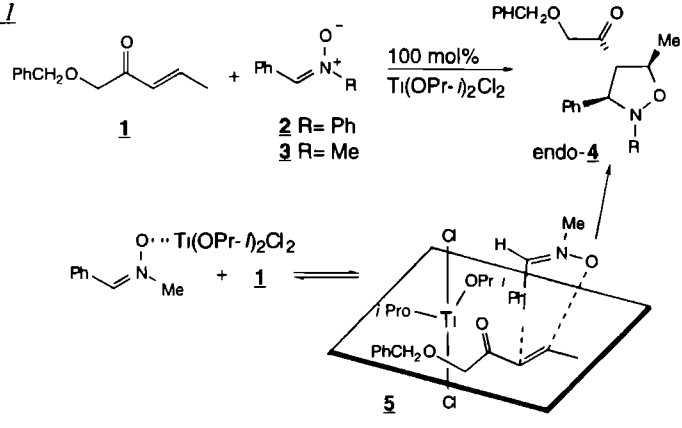
Figure 1 Case 1, dipole-HOMO controlled reaction Case 2, dipole-LUMO controlled reaction

In the absence of Lewis acids the reactivity is enhanced for dipolarophiles with electron withdrawing groups, e g methyl acrylate, as well as for dipolarophiles having electron donating groups, e g ethyl vinyl ether Hence, according to Fukui's frontier orbital concept, the 1,3-dipolar cycloaddition is controlled on the one hand by the HOMO (highest occupied molecular orbital) of the dipole and the LUMO (lowest unoccupied molecular orbital) of the dipolarophile, and on the other hand by the LUMO of the dipole and HOMO of the dipolarophile (Figure 1)[1g] Conceptually, the electron withdrawing property of Lewis acids can be utilized in both pathways by decreasing the energy gap between HOMO and LUMO of the reactants The dipolarophile, e g α,β-unsaturated carbonyl compound, can be activated by complexation with the Lewis acid, which lowers its LUMO energy, and results in reaction with the HOMO of the dipole (Case 1) This process is similar to the Lewis acid catalyzed Diels-Alder reaction of α,β-unsaturated carbonyl compounds with dienes (Chapter 2 and 7) Alternatively, the Lewis acid can complex with the dipole (nitrone) and decrease its LUMO energy A dipolarophile carrying an electron donating group, e g ketene acetals or alkyl vinyl ethers, will then give a reaction via its HOMO, because the energy gap between the dipolar LUMO and dipolarophile HOMO is smaller (Case 2)

The 1,3-dipolar cycloadditions of nitrones under classical thermal conditions are generally performed at high temperatures (> 100 °C) with long reaction times (several hours or days)[12] Elevated temperatures have the drawback that cycloreversions and (*Z*)-(*E*)-isomerization take place extensively, leading to isomerization of the cycloaddition product[1g] Application of Lewis acid catalysis might result in enhanced reaction rates at lower temperatures and better regio- and stereoselectivity, as was found for Lewis acid catalyzed Diels-Alder reactions Eventually, enantiofacial discrimination of the dipolarophile (α,β-unsaturated carbonyl compound) or the nitrone by a *chiral* Lewis acid catalyst may allow the smooth introduction of chirality in the cycloadduct

The Lewis acid catalyzed 1,3-dipolar cycloaddition of α,β-unsaturated compounds is, at first glance, the most promising reaction to study because of the numerous examples of successful Lewis acid catalyzed Diels-Alder reactions of α,β-unsaturated compounds with dienes

Scheme 1



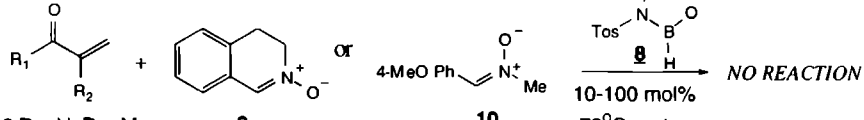
To overcome the difficulty that inactive nitrone/Lewis acid complexes will be formed, Kanemasa *et al* [4] designed electron-deficient olefinic dipolarophiles that have a chelate ligand structure, such as (*E*)-benzyloxy-3-penten-2-one **1** (*Scheme 1*) The 1,3-dipolar cycloadditions of **1** with C,N-diphenylnitrone **2** and C-phenyl-N-methylnitrone **3** were strongly catalyzed by Lewis acids, e g $Ti(OPr\text{-}i)Cl_2$, resulting in increased stereo- and regioselectivity The formation of the dipolarophile/Lewis acid complex **5** was proposed to be responsible for this first example of Lewis acid-catalyzed LUMO-dipolarophile-controlled nitrone cycloaddition Very recently, Murahashi *et al* [2a] used $ZnCl_2$ as a chelating Lewis acid in an asymmetric 1,3-dipolar cycloaddition of cyclic nitrones with chiral crotonates under high pressure (10 kbar) Although the reactivity decreased by complexation of $ZnCl_2$ to the nitrone as well as to the dipolarophile, the stereoselectivity was enhanced Tamura *et al* [2h,i] reported that the tandem esterification, intramolecular 1,3-dipolar cycloaddition of α-methoxycarbonylnitrones with allyl alcohols was accelerated in the presence of titanium isopropoxide to provide stereocontrolled polycyclic compounds in one step

3.2 Results and Discussion

3.2.1 LUMO-dipolarophile controlled cycloadditions catalyzed by Lewis acids

The successful application of chiral 1,3,2-oxazaborolidines[5], derived from N-sulfonylated amino acids[6], in asymmetric Diels-Alder reactions of α,β-enals, as described in Chapter 2, prompted us to study the use of these catalysts in 1,3-dipolar cycloaddition of nitrones with α,β-unsaturated carbonyl compounds, e g methacrolein **6** and methyl acrylate **7** (*Scheme 2*) Cyclic nitrone **9**[7] was selected because of its high reactivity in various cycloadditions Unfortunately, in the presence of 10 to 100 mol% chiral oxazaborolidine **8**, derived from N-tosyl *L*-isoleucine and BH_3-THF, no 1,3-dipolar cycloaddition occurred with this nitrone (**9**) and neither with C-(4-MeO-phenyl)-N-methyl-nitrone **10**[1h] at temperatures varying from -78 °C to room temperature

Scheme 2



6 R_1=H, R_2=Me
7 R_1=OMe, R_2=H

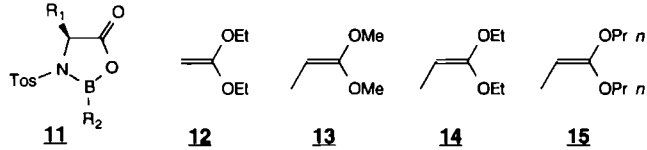
9

10

This lack of reactivity can probably be ascribed to the preferential complexation of the chiral oxazaborolidine to the nitrones, which obviously are stronger Lewis bases than the α,β-unsaturated carbonyl compounds The LUMO energies of these nitrones are decreased and no reactions occur with electron-poor dipolarophiles such as **6** or **7**

3.2.2 LUMO-nitrone controlled cycloadditions catalyzed by chiral oxazaborolidines

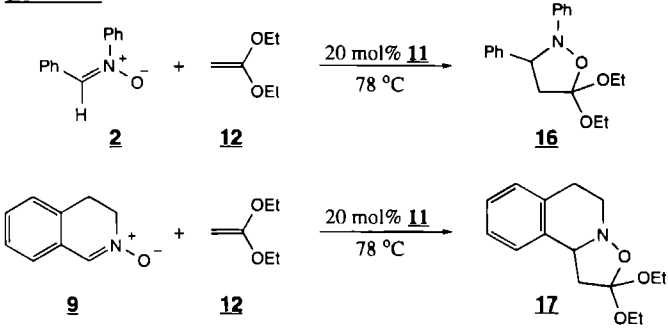
The results described in section 3 2 1 suggest that (chiral) Lewis acid catalysts may activate the nitrone by complexing to the oxygen atom of this molecule and thereby lowering the LUMO energy We rationalized that an electron-rich alkene (e g ketene O,O-dialkyl acetal[8,9] or enol ether[10,11]) might give a LUMO(nitrone) - HOMO(alkene) controlled 1,3-dipolar cycloaddition with enhanced reaction rate We decided to test chiral oxazaborolidines **11**, derived *in situ* from cheap and easily available N-tosyl-*L*-α-amino acids[5,6], as Lewis acid catalysts Our experiments were initially directed to 1,3-dipolar cycloadditions of C-phenyl-N-phenyl nitrone **2** and the more reactive and rigid 3,4 dihydroisoquinoline N-oxide **9**[7] with various ketene-O,O-acetals **12**-**15**[12]



11 **12** **13** **14** **15**

It has been reported that the 1,3-dipolar cycloadditions of nitrones **2** and **9** with 1,1 diethoxyethene **12** require high temperatures to proceed quantitatively[8a,b] We found that at room temperature these cycloadditions were very slow but could be catalyzed by several non-chiral Lewis acids, e g 20 mol% $EtAlCl_2$, Et_2AlCl, $ZnCl_2$ and ZnI_2 The use of ZnI_2 gave the corresponding 5,5-dialkoxyisoxazolidine with high regioselectivity in quantitative yield after two days A strong accelerating effect on the reaction was also observed with 20 mol% of the chiral oxazaborolidine **11** (R_2 = H) The reactions of nitrones **2** and **9** with ketene acetal **12** proceeded with complete regioselectivity and were complete after 24 and 5 hours, respectively, at -78 °C After aqueous workup the 5,5-dialkoxyisoxazolidines **16** or **17** were isolated as the only products (*Scheme 3*, Table 1) Enantioselectivities were determined by HPLC analysis using chiral columns Daicel CHIRALCEL OD and CHIRALPAK AD (Table 1)

Scheme 3



2 **12** **16**

9 **12** **17**

In order to study systematically the factors controlling the enantioselectivity we varied the side-chain substituent (R_1) of the oxazaborolidine and the substituent at the boron atom (R_2) One of our objectives was to find out whether the position of a phenyl ring in side-chain substituent R_1

would effect the enantioselectivity in a similar way as was found for the Diels-Alder reaction of acroleines with cyclopentadiene (Chapter 2)[5a] The reactivity of the chiral oxazaborolidines **11** appeared to be strongly dependent on the boron substituent BH_3-THF derived oxazaborolidines (R_2 = H) gave quantitative conversion of the two nitrones at -78 °C in dichloromethane The less acidic *n*-butyl-boron substituted oxazaborolidines (R_2 = *n*-Bu), which were derived *in situ* from *n*-butylboronic acid in propionitrile in the presence of 4Å molecular sieves, gave low conversion of nitrone **2** (*ca* 10%, entry 2) but were still strong enough to catalyze the 1,3-dipolar cycloadditions of the more reactive cyclic nitrone **9** at -78 °C (entries 6, 7, and 8) Despite the observed loss in reactivity, the enantioselectivity with nitrone **2** was dramatically higher with this *n*-butyl-boron substituted oxazaborolidine than with the hydrogen-substituted oxazaborolidine (entry 2 *vs* entry 1) In order to combine maximum reactivity with high enantioselectivity a substituent (R_2) at the boron atom was required other than hydrogen but with more electron withdrawing capacity than the *n*-butyl group Chiral oxazaborolidines, derived from 3,5-bis(trifluoromethyl)phenylboronic acid[13] in propionitrile in the presence of 4Å molecular sieves, gave quantitative conversion of nitrone **2** at -78 °C with low to moderate enantioselectivies (entries 3, 4 and 5)

Table 1 Catalytic asymmetric 1,3-dipolar cycloaddition of nitrones **2** and **9** with ketene acetal **12** mediated by chiral oxazaborolidines **11**[a] (Scheme 3)

entry	nitrone	side-chain substituent R_1	boron substituent R_2	isoxazolidine	e e (%)[b]
1	**2**	(4-(BzlO)-Ph)CH_2	H	**16**	4
2		(4-(BzlO)-Ph)CH_2	*n*-Bu		74[c]
3		Ph	3,5-$(CF_3)_2$Ph		0
4		$PhCH_2$	3,5-$(CF_3)_2$Ph		44
5		(4-(BzlO)-Ph)CH_2	3,5-$(CF_3)_2$Ph		44
6	**9**	Ph	*n*-Bu	**17**	12[d,e]
7		$PhCH_2$	*n*-Bu		12
8		(4-(BzlO)-Ph)CH_2	*n*-Bu		6
9		$PhCH_2OCH_2$	H		14[d]
10		indolyl-CH_2	H		4[e]
11			*n*-Bu		10[e]

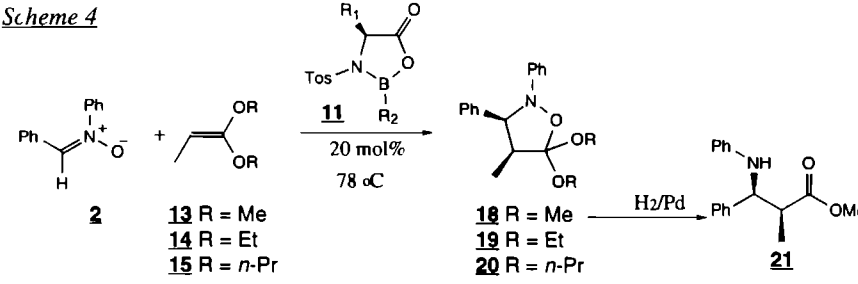
[a] All reactions were performed in dichloromethane (R_2 =H) or in propionitrile (R_2=*n* Bu 3 5 $(CF_3)_2$Ph) at 78 °C Reaction time ca 5 24 hrs untill quantitative conversion of the nitrone was achieved absolute configuration of the products is unknown [b] Determined by HPLC (Chiralcel OD and Chiralpak AD) *n* hexane/*i* PrOH 98/2 (v/v) [c] Chemical yield at room temperature in propionitrile is ca 10% [d] Reaction in tetrahydrofuran [e]Reversal of enantioselectivity is observed

Table 1 shows that for nitrone **2**, apart from the boron substituent in the oxazaborolidine, the enantioselectivity also seems to depend on the position of a phenyl ring in the side-chain substituent (R_1) of the chiral oxazaborolidine The best results (44% ee) were achieved in

propionitrile with oxazaborolidines derived from *L*-phenylalanine and *L*-tyrosine-(O-benzyl ether) with R_1 = $PhCH_2$ and (4-(BzlO)-Ph)CH_2, respectively, and R_2 = 3,5-$(CF_3)_2$Ph (entries 4 and 5) The enantioselectivities found with the cyclic nitrone **9** were disappointingly low The oxazaborolidines derived from *L*-phenylglycine (entry 6) and *L*-tryptophane (entries 10 and 11) gave a slight reversal of enantioselectivity compared to the *L*-phenylalanine- (entry 7), *L*-tyrosine(O benzyl ether)- (entry 8) and *L*-serine(O-benzyl ether)-derived oxazaborolidines (entry 9) The position of a phenyl group in the side-chain substituent R_1 obviously has no effect on the enantioselectivity with nitrone **9** The possible effect of the various solvents tested, i e dichloromethane, tetrahydrofuran or propionitrile, on the enantioselectivity is not yet clear[14]

The reactivity, regio-, stereo- and enantioselectivity of monosubstituted ketene acetals, e g 1,1-dialkoxy-propenes **13**, **14** and **15** in the chiral oxazaborolidine catalyzed 1,3-dipolar cycloaddition with acyclic nitrone **2** were studied next These ketene acetals were expected to be less reactive than unsubstituted ketene acetals, but more stable towards oligomerization processes Furthermore, the presence of a prochiral center in these ketene acetals could lead to a mixture of *cis*- and *trans*-isoxazolidine diastereomers In the presence of 20 mol% of chiral oxazaborolidines **11** nitrone **2** was completely converted after 24 hours at -78 °C (*Scheme 4*, Table 2)

Scheme 4



2

13 R = Me
14 R = Et
15 R = *n*-Pr

18 R = Me
19 R = Et
20 R = *n*-Pr

21

Table 2 Catalytic asymmetric 1,3-dipolar cyloaddition of C,N-diphenyl nitrone **2** with ketene acetals **13**-**15** mediated by chiral oxazaborolidines **11**[a]

entry	ketene acetal	side-chain substituent R_1	boron substituent R_2	isoxazolidine	e e (%)[b]
1	**13**	Ph	H	**18**	5
2		(4-(BzlO)-Ph)CH_2	H		11
3	**14**	Ph	H	**19**	20[c]
4		$PhCH_2$	H		50
5		$PhCH_2CH_2$	H		10
6		(4-(BzlO)-Ph)CH_2	H		62
7		(4-(BzlO)-Ph)CH_2	3,5-$(CF_3)_2$Ph		4
8	**15**	(4-(BzlO)-Ph)CH_2	H	**20**	55

[a] All reactions were performed in dichloromethane (R_2 =H) or in propionitrile (R_2 = 3,5 $(CF_3)_2$Ph) at 78 °C for ca 5 24 hrs until quantitative conversion of the nitrone was observed absolute configuration of the products is unknown [b] Determined with HPLC (Chiralcel OD and Chiralpak AD) eluent *n* hexane/*i* PrOH 99/1 (v/v) [c] Reaction was carried out in THF

The reactions proceeded with complete regioselectivity to afford the 4-methyl-5,5-dialkoxyisoxazolidines **18**, **19** and **20** as single diastereomers (the absolute configuration is arbitrarily chosen) Only the *cis*-isoxazolidines were formed, as was confirmed by ^{1}H-NMR (coupling constant between H-3 and H-4 in **18** J = 7 0 Hz, and in **19** J = 6 9 Hz) The corresponding *trans*-isoxazolidines are expected to have lower coupling constants[11] Further evidence for *cis*-stereoselectivity was obtained after mild hydrogenolysis of the N-O bond in *cis*-**18** (1 atm H_2/Pd, 30 min room temperature) to yield the known *syn*-β-amino ester **21**, which displayed the following coupling constant $J_{H2,H3}$ = 5 0 Hz[15a] A similar coupling constant ($J_{H2\,H3}$ = 5 2 Hz) was found for the *syn*-β-amino ester derived from **19** or **20** The *anti*-β-amino ester corresponding to **21** is known in the literature and was prepared by a TMSOTf-catalyzed reaction of silyl ketene acetal with imines[15c] The results in Table 2 further show that the enantioselectivity is dependent on the structure of the ketene acetal, the position of a phenyl group in the side-chain substituent R_1 and the substituent R_2 on the boron atom

For 1,1-dimethoxypropene **13** only poor enantioselectivities were obtained in the two experiments that were carried out (entries 1 and 2) Ketene acetals **14** and **15** with larger alkoxy groups showed a similar behaviour as found for ketene acetal **12** with respect to the position of a phenyl group in substituent R_1 of the chiral oxazaborolidine (entry 6 and 8) A phenyl group at position 2 in side-chain substituent R_1 is essential to obtain a reasonable enantioselectivity A similar result was already found for the asymmetric Diels-Alder reaction of α,β-enals[5a] (see Chapter 2) For 1,1-diethoxypropene **14** best enantioselectivities were found with oxazaborolidines derived from *L*-phenylalanine or *L*-tyrosine(O-benzyl ether) and BH_3 THF (R_2 = H) in dichloromethane (entries 4 and 6) The enantioselectivity dropped dramatically in propionitrile when an aryl substituted boron substituent was used (entry 7, R_2 = 3,5-$(CF_3)_2$Ph) The role of the solvent, dichloromethane (plus *ca* 12 equiv THF from BH_3-THF during catalyst preparation, entry 6) versus propionitrile, (in the presence of 4Å molecular sieves, entry 7) is not yet clear In Chapter 4 of this thesis we will discuss and evaluate in more detail the effects of donor solvents on the enantioselectivity of chiral oxazaborolidine catalyzed 1,3 dipolar cycloadditions of nitrones with ketene acetals

Chiral oxazaborolidine catalyzed 1,3-dipolar cycloaddition of 1,1-dialkoxypropenes **13**-**15** with cyclic nitrone **9** with a rigid *E*-configuration gave regio- and stereoselectively the *cis*-4-methyl-5,5-dialkoxyisoxazolidines **22**, **23** and **24** in a quantitative yield (*Scheme 5, Table 3*) The *cis*-stereochemistry assigned to these isoxazolidines is based on NMR and NOESY studies Most relevant is the large coupling constant between H-3 and H-4 (**22** J = 9 9 Hz, **23** J = 10 2 Hz, **24** J = 10 3 Hz) and the presence of NOE interactions between H-3 and H-4

The trends in R_1-dependent enantioselectivity observed for 1,3-dipolar cycloaddition of nitrone **2** with ketene acetals **13**-**15** are less pronounced in the case of cyclic nitrone **9** However, for oxazaborolidines derived from *n*-butylboronic acid in propionitrile the position of the phenyl group in the side-chain substituent R_1 seems to determine the enantioselectivity (entries 3, 5 and 8) Again, the tyrosine(O-benzyl ether)-derived oxazaborolidine (R_1 = (4-(BzlO)-Ph)CH_2, R_2=*n*-

Bu) gives the best enantioselectivities with each ketene acetal (entry 8, 12 and 14) up to 44% ee for isoxazolidine **22**. The size of the alkoxy group in the ketene acetal seems to have a small effect on the enantioselectivity, in contrast to the reactions with the acyclic nitrone **2**. Typically, 1,1-dimethoxypropene **13** gives better results with the cyclic nitrone **9** than with the acyclic nitrone **2**. Chiral oxazaborolidines with a hydrogen-substituted boron atom (R_2 = H) instead of *n*-Bu (R_2 = *n*-Bu) gave lower enantioselectivities (*ca.* 4-12% ee) in dichloromethane in all cases.

Scheme 5

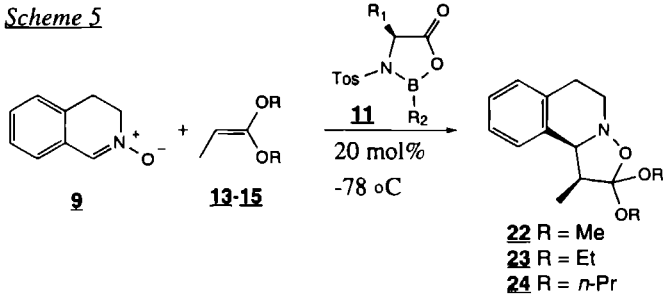


Table 3. Catalytic asymmetric 1,3-dipolar cyloaddition of 3,4-dihydroisoquinoline N-oxide **9** with ketene acetals **13**-**15**[a]

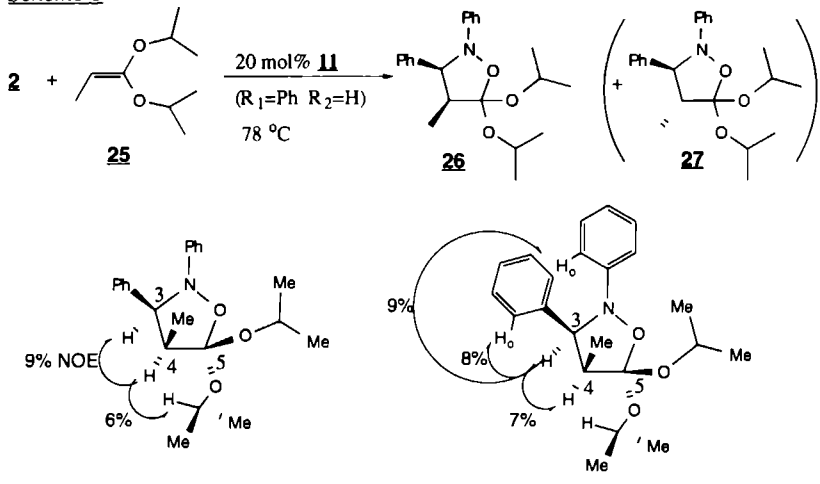
entry	ketene acetal	side-chain substituent R_1	boron substituent R_2	isoxazolidine	e.e. (%)[b]
1	**13**	Ph	H	**22**	12
2		$PhCH_2$	H		10
3			*n*-Bu		24
4		$PhCH_2CH_2$	H		6
5		(4-(MeO)-Ph)CH_2	*n*-Bu		36
6		(4-(BzlO)-Ph)CH_2	H		4
7			*n*-Bu[c]		9
8			*n*-Bu		44
9			Ph		18
10	**14**	(4-(BzlO)-Ph)CH_2	H	**23**	12
11		$PhCH_2$	*n*-Bu		20
12		(4-(BzlO)-Ph)CH_2	*n*-Bu		22
13		$BzlOCH_2$	*n*-Bu		20
14	**15**	(4-(BzlO)-Ph)CH_2	*n*-Bu	**24**	39

[a] All reactions were performed in dichloromethane (R_2 =H) or in propionitrile (R_4 =*n*-Bu, Ph) at -78 °C for *ca* 5-24 hrs until quantitative conversion of the nitrone was obtained, absolute configuration of the products is arbitrarily chosen , [b] Determined HPLC (Chiralcel OD and Chiralpak AD), eluent *n*-hexane/*i*-PrOH 99/1 (v/v), [c] Reaction performed in dichloromethane

The important role of the solvent was demonstrated with *n*-butyl substituted oxazaborolidine (R_2 = *n*-Bu) derived from tyrosine(O-benzyl ether) The switch from the polar solvent propionitrile to dichloromethane in the catalyst preparation and subsequent 1,3-dipolar cycloaddition reaction gave a drop in enantioselectivity from 44% to only 9% ee (entry 8 *vs* 7)

Thus far, the chiral oxazaborolidine catalyzed 1,3-dipolar cycloaddition of nitrones **2** and **9** with ketene acetals **12**-**15** have demonstrated that high reactivity is combined with complete regio and *cis*-stereoselectivity In order to further explore the scope of this reaction other ketene acetals and nitrones were tested For example, the chiral oxazaborolidine catalyzed 1,3-dipolar cycloaddition of **2** with bulky ketene acetal **25** gave a mixture of *cis*-isoxazolidine **26** and some unidentified products after 20 hours (*Scheme 6*) The formation of the corresponding *trans*-isoxazolidine **27** during the reaction could not be established, because it was not isolated After chromatography only *cis*-**26** was isolated in a pure state and in 73% yield

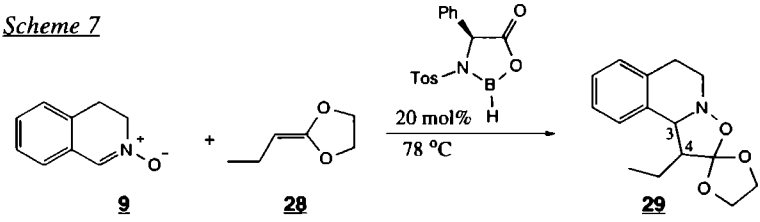
Scheme 6



The relative stereochemistry in compound **26** was established by NOE Difference NMR spectroscopy It was shown that H-3 is in the vicinity of H-4 (9% NOE enhancement) and the hydrogen atom at the tertiary carbon atom of the α-5-isopropoxy group (6% NOE effect) In addition, H-3 appeared to be proximate to the *ortho* protons of both phenyl groups which indicates that the N-phenyl group is probably oriented *anti* to the C-phenyl group This would imply that the nitrogen atom does not invert itself due to a "fixed sp^3-character Further evidence for the *cis*-stereochemistry was provided by conversion of **26** to the corresponding β-amino ester by reductive cleavage of the N-O bond The coupling constant of 5 4 Hz between protons H-2 and H-3 in the resulting product indicates the *cis*-relationship, in a similar way as in the case of **21** Unfortunately, it was not possible to determine the enantioselectivity of the cycloaddition reaction in this case by HPLC using chiral columns Daicel Chiralcel OB, OD or ChiralPak AD

The 1,3-dipolar cycloaddition of nitrone **9** with dioxolane-type ketene acetal **28**[16] in the presence of 20 mol% of *L*-phenylglycine derived oxazaborolidine **11** (R_1=Ph, R_2=H) gave a poor conversion after 22 hours, probably due to the rigid alkoxy functionalities of the ketene acetal (*Scheme 7*) A mixture of products was obtained, of which only the *cis*-product **29** could be isolated in 20% yield after purification by chromatography The *cis*-stereochemistry was assigned on the basis of the coupling constant J = 8 2 Hz between H-3 and H-4 Again, it was not possible to determine the enantioselectivity by HPLC using chiral columns These results suggest that the size and flexibility of the alkoxy group in the ketene acetal influences both the reactivity as well as the stereoselectivity of the cycloaddition

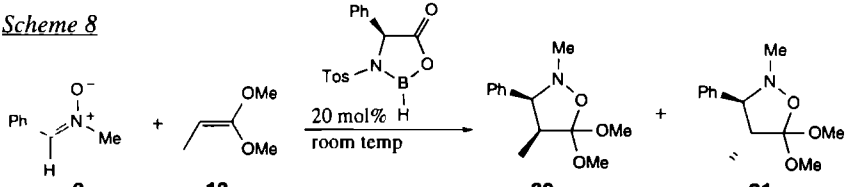
Scheme 7



9 **28** **29**

Further exploration of the chiral oxazaborolidine catalyzed 1,3-dipolar cycloaddition reaction was done with acyclic N-methyl and N-benzyl nitrones, **3** and **32**, respectively The reaction of C-phenyl N-methyl nitrone **3** with 1,1-dimethoxypropene **13** was catalyzed by 20 mol% *L*-phenylglycine-derived oxazaborolidine **11** at room temperature to give a 50/50 mixture of *cis*-**30** and *trans*-**31** in 63% isolated yield At -78 °C or 0 °C almost no conversion of the nitrone was observed

Scheme 8

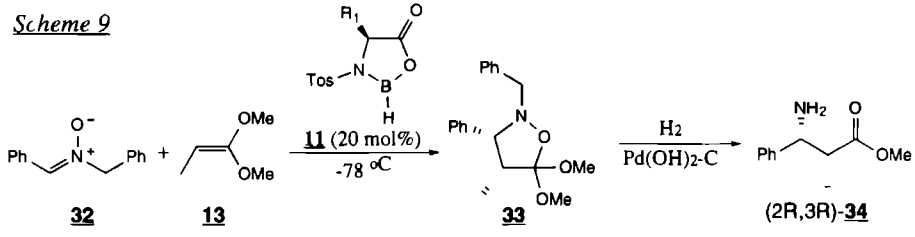


3 **13** **30** **31**

The application of N-benzyl nitrones[17] in a 1,3-dipolar cycloaddition strategy towards natural products is of particular interest because by simple debenzylation a primary amino function can be installed in the molecule Chapter 6 of this thesis deals with the application of chiral oxazaborolidine catalyzed 1,3-dipolar cycloadditions in the synthesis of β-amino esters The reaction of C-phenyl-N-benzyl nitrone **32** with ketene acetal **13** was found to be strongly catalyzed by 20 mol% chiral oxazaborolidines **11** in dichloromethane at -78 °C to give regio- and stereoselectively the corresponding *cis*-2 benzyl 3-phenyl-4-methyl-5,5-dimethoxy-isoxazolidine **33** in quantitative yield (*Scheme 9*, Table 4) The relative and absolute stereochemistry of **33** was established by converting the cycloadduct via one-step hydrogenolysis with hydrogen on $Pd(OH)_2$-carbon (Pearlman s catalyst[18]) to the known *syn*-(*2R,3R*)-β-amino ester **34**[19a,b] The *syn*-selectivity

was also determined by ^{1}H-NMR experiments A ^{1}H-NMR coupling constant $J_{H2,H3}$ = 5 9 Hz was observed for **34** which is typical for *syn*-β-amino esters of this type The corresponding *anti*-diastereomer of β-amino ester **34** was reported to have a ^{1}H-NMR coupling constant $J_{H2\,H3}$ = 9 5 Hz[19c] The optical purity of **34** was determined by HPLC on a Chiralcel OD column Modification of the amino ester **34** with (*R*)-Mosher chloride[20] provided a mixture of the corresponding diastereomeric Mosher-amides **35a** and **35b** (*Scheme 10*) GC-analysis, ^{1}H- and ^{19}F-NMR analysis of these diastereomers gave reproducible enantioselectivities with the same results as HPLC Table 4 shows that the tyrosine(O-benzyl ether)-derived oxazaborolidine (R_1 = (4-(BzlO)-Ph)CH_2) which gave the best enantioselectivities for the reactions of nitrones **2** and **9** with ketene acetal **12**-**15** is not the best chiral catalyst in the present case (0% ee, entry 5) The highest enantioselectivity (59% ee) was obtained with a *L*-homophenylalanine-derived oxazaborolidine (entry 4) Remarkably, the position of the phenyl group in homophenylalanine is quite similar to the position of the phenyl moiety in tryptophane (R_1= indolyl-CH_2, entry 6) for which similar enantioselectivity was found The isoleucine-derived oxazaborolidine (entry 1), lacking a phenyl group in the side-chain substituent gave, however, almost the same enantioselectivity

Scheme 9



Scheme 10

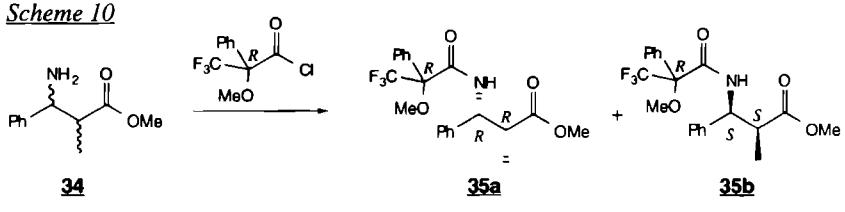
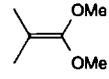


Table 4 Enantioselective 1,3-dipolar cycloaddition of nitrone **32** with ketene acetal **13** catalyzed by chiral oxazaborolidines **11** (*Scheme 9*)

entry	side-chain substituent R_1 in **11**	e e **34** (%)
1	*i*-Bu	45
2	Ph	17
3	$PhCH_2$	11
4	$PhCH_2CH_2$	59
5	(4-($PhCH_2O$)-$PhCH_2$	0
6	indolyl-CH_2	46

It is not clear whether in the asymmetric 1,3-dipolar cycloaddition of nitrone **32** with ketene acetal **13** the enantioselectivity is controlled by the position of a phenyl group in the substituent R_1 in **11** (via π-π attractive interactions) or by steric hindrance The low enantioselectivities observed for phenylalanine-type oxazaborolidines with R_1 = $PhCH_2$ (entry 3) and R_1 = (4-benzyloxy)-$PhCH_2$ (entry 5) could be the result of two competing interactions, i e attractive π-π vs steric interactions Remarkably, in the asymmetric Diels-Alder reaction of 2-bromoacrolein high enantioselectivity was observed with both the tryptophane-derived and the tyrosine-derived oxazaborolidine as the result of attractive π-π interactions[5a] The fact that these catalysts give quite different selectivities with nitrones indicates that the chiral recognition process obviously depends on the structure of the prochiral substrates

The straightforward syntheses of β-amino esters **21** and **34** demonstrate that the catalytic asymmetric 1,3 dipolar cycloaddition of nitrones with ketene acetals provides a simple route to chiral β-amino esters This will be discussed further in Chapter 6 of this thesis

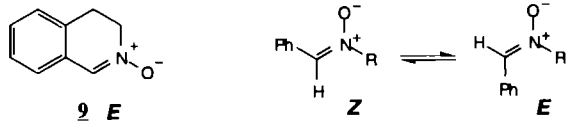


35

Finally, it is worth mentioning that in the presence of chiral oxazaborolidines **11** ketene acetal **35** was not reactive with the nitrones **2**, **3**, **9** or **32** in the temperature range -78 °C - room temperature, probably due to severe steric hindrance in the transition state of the reaction[9]

3.2.3 Mechanisms of the 1,3-dipolar cycloaddition. Stereochemical considerations.

To explain the configurational relationships found for the stereoselective formation of the *cis*-4-alkyl-3-aryl-isoxazolidines the mechanism of the cycloaddition needs to be known Much attention has been paid in the literature to the problem of the timing of the bond formation, i e whether the cycloaddition takes place via a concerted reaction (with synchronous or non-synchronous bond formation) or via a dipolar intermediate[1] Analogous to the *endo/exo* approach in the Diels-Alder reaction secondary orbital interactions can stabilize the transition state and favour the formation of one of the two possible adducts For the design of new chiral Lewis acid catalysts for 1,3 dipolar cycloadditions of nitrones with electron-rich alkenes elucidation of the exact structure of the nitrones and their Lewis acid complexes in solution is crucial Acyclic nitrones can exist in the *Z*- and/or the more reactive *E*-configuration



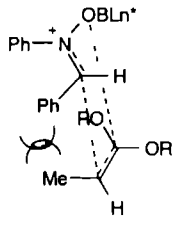
9 ***E*** ***Z*** ***E***

R = Me Ph, CH_2Ph

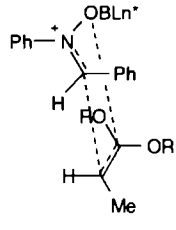
Figure 2 *E*- and *Z*-nitrones

The dynamic equilibria between these isomers can influence the stereochemistry of the 1,3-dipolar cycloaddition It is well known that *E*-nitrones, e g dihydroisoquinoline N-oxide **9**, are far more reactive than their *Z*-counterparts in concerted [3+2]-cycloaddition reactions The rotation barrier for most nitrones usually is so high, $E_a \geq 30$ kcal mol $^{-1}$, that the nitrones are completely stable at reaction temperatures below 80 °C and reaction times less than 24 h[1g] commonly applied Besides higher temperatures, e g in refluxing xylene, or electron withdrawing groups at C_α, nitrones can also undergo photochemical and acid-catalyzed *cis-trans* (*E-Z*) isomerization[21]

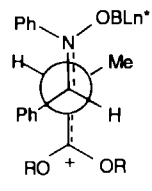
Exclusive formation of *cis*-isoxazolidines was found for reactions with the acyclic nitrones **2** and **32** (mixtures of *E* and *Z* ?)[22] and the cyclic *E*-nitrone **9** Extensive NMR and NOESY investigations showed that the BF_3-complexes of C-phenyl-N-phenyl nitrone and C-phenyl-N-benzyl nitrone in $CDCl_3$ solution and at low temperatures exist as a dynamic mixture of *E*- and *Z*-isomers[23] A priori, the stereoselective formation of the *cis*-5,5-dialkoxy-4-methyl-3-phenyl isoxazolidines can be rationalized by a concerted 1,3-dipolar cycloaddition mechanism in which the *E*-nitrone reacts via an *endo* transition state **I** and the *Z*-nitrone reacts via an *exo* transition state **II** The found stereoselectivity is also in accordance with dipolar transition states **III** and **IV** arising from the most favourable transoid approach of the ketene acetal to the *E*- or *Z*-nitrone moiety, as described analogously for the polar [2+2]-cycloaddition of ketene acetals to carbonyl compounds or electron-poor imines[24]



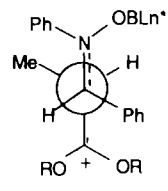
I endo-*E*



II exo-*Z*



III dipolar-*E*



IVdipolar-*Z*

The concerted (non-synchronous) *endo*-selective approach **I** of the ketene acetal to the *E*-nitrone has no possibility for secondary orbital interactions and will be disfavoured by steric hindrance between the C-phenyl and N-phenyl group of the nitrone and the methyl group of the ketene acetal The *exo* approach **II** to the *Z*-nitrone will also suffer from steric hindrance between the C-phenyl group of the nitrone and the methyl group of the ketene acetal Therefore, a concerted mechanism is less likely As illustrated in Figure 2 for *E*-nitrones, the most favourable transoid approach of the ketene acetal to the complexed nitrone as depicted in **B** will lead to the *cis*-cycloadduct via rotation to gauche intermediate **B''** The sterically less favored approach of the ketene acetal to the nitrone as represented by **A** will lead to the thermodynamically more stable *trans*-cycloadduct The *trans* adduct is therefore expected if the cycloaddition is thermodynamically controlled High stereoselectivity in polar [2+2] cycloadditions of 1,1-dialkoxypropenes is only found when the reaction proceeds under kinetic control (e g , low reaction temperatures)[24] At higher temperature

the reaction becomes thermodynamically controlled and the *cis* stereoselectivity decreases, as is evidenced by the poor stereoselectivity (*ca* 50/50 *cis/trans*) observed for C-phenyl-N-methyl nitrone **3** at room temperature

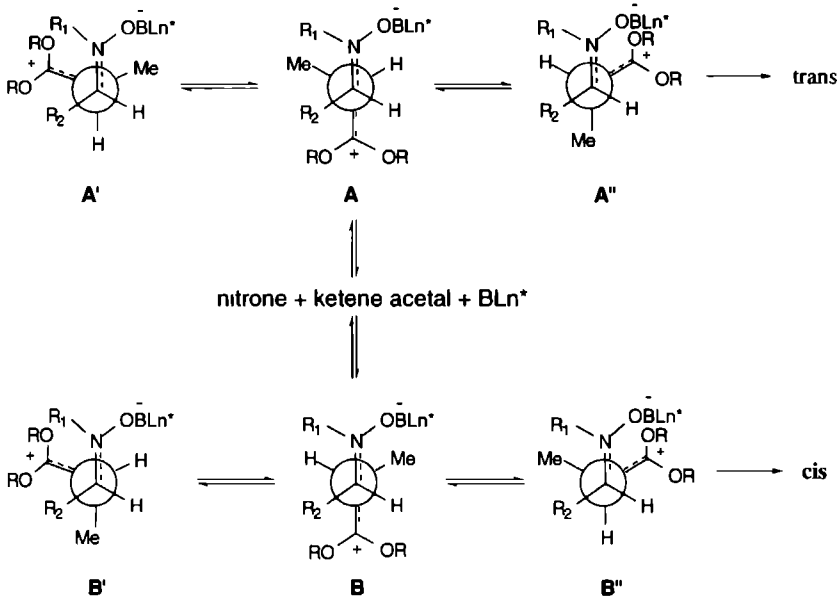


Figure 2 Newman projections of dipolar intermediates

For a detailed understanding of the chiral recognition mechanism, i e enantiofacial discrimination of the nitrone, first the spatial orientation of the reactants in the transition state needs to be known The conformational restrictions and rotation barriers, for example, rotation around the B-O, O-N, and N-R bond in the chiral Lewis acid-nitrone complex are of crucial importance for effective enantioface shielding of the nitrone

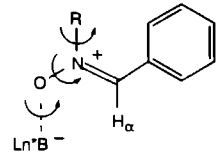
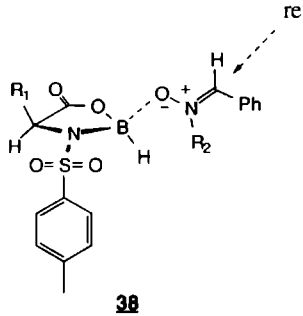


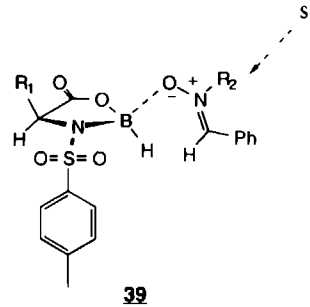
Figure 4

For this reason it will be clear that rationalizations for the observed enantioselectivities and the understanding of the chiral recognition mechanism by means of transition state models, i e working models, are very difficult From the results with C-phenyl-N-benzylnitrone **32** we have deduced "working models" **38** and **39** to represent the configurational relationships between the chiral oxazaborolidines and the obtained products The three-dimensional arrangement of the chiral oxazaborolidine is expected to be the same as was described for the asymmetric Diels Alder

reaction[5] Because most reactions were carried out in dichloromethane containing THF the oxazaborolidine is expected to be a monomeric species The chiral center directs the steric bulk of the N-sulphonyl part to the opposite side of the ring The observed enantioface selectivities can be explained based on the following assumptions (i) the nitrone, in its more reactive *E*-configuration[20], is complexed with the boron via the basic oxygen atom, (ii) all substituents of the oxazaborolidine ring are now positioned as far as possible from each other, (iii) the conformers **38** and **39**, obtained by rotation around the B-O, O-N and N-R_2 bonds of the *E*-nitrone part, are expected to be the more stable ones



38



39

The models explain that for C-phenyl-N-phenylnitrone **2** (R_2 = Ph) low enantioselectivity is found in case where R_1 operates as a sterically demanding group, because the chiral center is too far away from the nitrone reaction center Attractive π-π interactions between the side-chain substituent R_1 (for R_1 = 4-(BzlO)-$PhCH_2$) and the iminium part of nitrone can increase the enantioselectivity probably via a nitrone orientation as presented in model **39** Unfortunately, the absolute configuration of the chiral cycloadducts of C-phenyl-N-phenylnitrone are unknown which does not allow to draw further conclusions about the transition state For C-phenyl N-benzylnitrone **32** the situation is more complicated Inspection of molecular models of the oxazaborolidine-nitrone complex clarifies that the flexible benzylic group (R_2= $PhCH_2$) is able to participate in shielding one of the two faces of the nitrone by rotation around the N-CH_2 bond The complexicity of the system and the differences in enantioselectivities observed for nitrone **2** and **32** using a given catalyst do not allow to speculate more about the transition state In Chapter 4 of this thesis further details are presented

3.3 Conclusions

From the results described in this chapter some important conclusions can be drawn on catalytic asymmetric 1,3-dipolar cycloadditions of nitrones

1) Chiral 1,3,2-oxazaborolidines are good Lewis acid catalysts (10-20 mol%) for (asymmetric) 1,3-dipolar cycloadditions of various (a)cyclic nitrones with ketene acetals at low temperatures This is the first example of chiral Lewis acid catalysis in nitrone cycloadditions with electron-rich alkenes

2) The reactions proceed in high yields with complete regioselectivity to give the corresponding 5,5 dialkoxyisoxazolidines
3) Monoalkylated ketene acetals, e g 1,1-dialkoxypropenes, react with complete stereoselectivity to give exclusively *cis*-isoxazolidines which can be transformed in one step to the corresponding *syn*-β-amino esters
4) The enantioselectivity of the cycloaddition strongly depends on the structures of the nitrone and the ketene acetal, and the boron-substituent
5) C-phenyl-N-phenylnitrone **2** gives highest enantioselectivities with chiral oxazaborolidines derived from *L*-phenylalanine or *L*-tyrosine(O-benzyl ether) Attractive π-π interactions between the side-chain substituent of these catalysts with nitrone **2** probably determine the enantioselectivity, C-phenyl-N-benzylnitrone **32** behaves in a more complicated way due to the extra rotational freedom of the N-benzyl group
6) The observed enantioselectivities can be partially explained with simplified models, analogously to the chiral oxazaborolidine catalyzed asymmetric Diels-Alder reactions as described in Chapter 2 of this thesis

3.4 Experimental Section

Dichloromethane was dried and distilled on CaH_2 and stored over 4Å molecular sieves All reactions were carried out under dry nitrogen or argon atmosphere ^{1}H-NMR spectra and ^{13}C-NMR were recorded on a Varian EM 390 (90 MHz, CW), a Bruker AM-100 (100 MHz, FT) or a Bruker AM-400 (400 MHz, FT) spectrometer with TMS as internal standard Decoupling experiments were run with DEPT 135 IR spectra were run on a Perkin-Elmer 298 spectrophotometer Mass spectra were measured with a Varian SM1-B double focussing mass spectrometer or with a VG 7070E mass spectrometer Gas chromatography was performed on a Hewlett-Packard 5710A GC-instrument equipped with a capillary HP cross-linked methyl silicone (25 m x 0 31 mm) column Purification of products was done by 'flash"-chromatography on silica gel, chromatography on basic alumina, a Miniprep LC instrument (Jobin Yvon) with Merck silicagel 60H as stationary phase, or a Chromatotron (Model 7924T, Harrison Research) with silicagel 60 PF_{254} (cont gypsum) as stationary phase Mixtures of diethyl ether/n-hexane (1 1-7, v/v) were used as eluent Enantioselectivities were determined with HPLC using chiral Daicel CHIRALCEL OB, OD and CHIRALPAK AD columns with hexane/2-propanol mixtures as eluent on a LKB 2225 HPLC apparatus with UV detection Racemic products obtained from ZnI_2 catalyzed reactions were used as reference materials for the determination of ee with HPLC The nitrones **2** and **3** were prepared by condensation of benzaldehyde with the corresponding hydroxylamines[1h], the nitrones **9** and **30** were prepared by oxidation of the corresponding secondary amines with H_2O_2/Na_2WO_6 according to literature procedures[7] The ketene acetals **12**-**15**, **23**, **26**, **33** and **34** were all prepared according to literature procedures[12,16] The synthesis of N tosyl α-amino acids and the *in situ* preparation of chiral 1,3,2-oxazaborolidines has been described before[5,6]

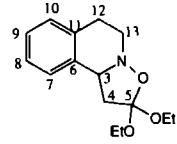
General procedure The chiral oxazaborolidines (0 2 mmol) were prepared *in situ* from N-tosyl-*L*-α–amino acids[6] at room temperature under a dry nitrogen atmosphere by addition of equimolar amounts of BH_3-THF, or *n*-$BuB(OH)_2$ or 3,5-$(CF_3)_2PhB(OH)_2$ in the presence of powdered 4Å molecular sieves, in dry solvent (4 ml) Nitrone (1 0 mmol) was added at room temperature, the mixture was cooled to -78 °C and the ketene acetal (2-3 eq) was added After completion of the reaction (5-24 hrs) the reaction mixture was quenched with saturated aqueous bicarbonate, extracted with dichloromethane and diethyl ether, dried (Na_2SO_4) and concentrated under vacuum The crude isoxazolidine was purified by flash chromatography on silica gel or alumina using ether *n*-hexane (1 1-4, v/v, containing *ca* 1% Et_3N) as eluent Yields ca 80-99%

2,3-Diphenyl-5,5-diethoxy-isoxazolidine 16[8a]

oil, 400 MHz ^{1}H NMR δ(ppm) 1 07 3H, t, J = 7 1 Hz, CH_3, 1 27, 3H, t, J = 7 1 Hz, CH_3, 2 51 1H, dd, J = 9 7 Hz, J_{gem} = 12 3 Hz, H4, 2 81, 1H, dd, J = 7 6 Hz, J_{gem} = 12 3 Hz, H4, 3 68 2H, q, J = 7 1 Hz, CH_2O, 3 76 2H, q, J = 7 1 Hz, CH_2O, 4 73 1H, dd, J = 7 6 Hz and J = 9 7 Hz, H3, 6 91 3H, m, ArH, 7 16 2H, m, ArH, 7 31 3H, m, ArH, 7 50 2H, m, ArH ^{13}C NMR δ(ppm) 15 0 (CH_3), 15 2 (CH_3), 46 0 (C-4), 58 0 (CH_2), 59 7 (CH_2), 69 8 (C-3), 115 4, 119 7 (C 5), 121 8, 126 7, 127 7, 128 4, 128 8, 140 9 (C_{ipso}), 151 1 (C_{ipso}) HRMS (rel int) m/e 313 (M^+, 3), 268 (16), 206 (14), 205 (100), 180 (14), 177 (16), 149 (16), 131 (45), 117 (14) Peak Match M_{calc} = 313 16779, M_{found} = 313 16783 ±0 00091 The enantioselectivity was determined by HPLC on a CHIRALPAK AD column, UV detection at 250 nm, flow rate 0 75 ml/min , eluent *n* hexane/2-PrOH = 98/2 (v/v), 8 22 min (major isomer) and 9 75 min (minor isomer)

5,5-Diethoxy-isoxazolidine 17

atom numbering



Oil, 400 MHz ^{1}H NMR δ(ppm) 1 16 3H, t, J = 7 1 Hz, CH_3, 1 26 3H, t, J = 7 1 Hz, CH_3, 2 50 1H, dd, J = 10 0 Hz, J_{gem} = 12 9 Hz, H-4, 2 77 1H, dd, J = 7 6 Hz, J_{gem} = 12 9 Hz, H 4, 2 92 1H, dt, $J_{H12\,H12}$ = 12 1 Hz, $J_{H12\,H13}$ = 4 1 Hz, $J_{H12\,H13}$ = 0 Hz, H 12, 2 98 1H, ddd, $J_{H12\,H13}$ = 5 1 Hz, $J_{H12\,H13}$ = 4 7 Hz, $J_{H12\,H12}$ = 12 1 Hz, H-12 , 3 37 1H, quintet, $J_{H13\,H12}$ = 0 Hz, $J_{H13\,H12}$ = 4 7 Hz, $J_{H13,H13}$ = 11 1 Hz, H-13, 3 47 1H, ddd, $J_{H13\,H12}$=4 1 Hz, $J_{H13,H12}$ = 5 1 Hz, $J_{H13\,H13}$ = 11 1 Hz, H-13', 3 68 2H, q, J = 7 1 Hz, CH_2, 3 76 2H, q, J = 7 1 Hz, CH_2, 4 88 1H, t, $J_{H3\,H4}$=$J_{H3\,H4}$ = 8 7 Hz, H-3, 7 10 4H, m, H-7, H-8, H-9 and H-10 ^{13}C NMR δ(ppm) 15 2 (C-15 and C-17), 28 0 (C-12), 43 7 (C-4), 49 1 (C-13), 58 1 (C-14), 59 1 (C-16), 62 4 (C-3), 123 4 (C 5), 126 3 (C-9), 126 6 (C 10), 127 0 (C-8), 128 3 (C-7), 133 3 (C-11), 135 3 (C-6) HRMS (rel int) m/e 264 (M^{+1}, 1), 263 (M^+, 7), 218 (-OEt, 6), 172 (-OEt, 8), 129 (100) Peak Match M_{calc} = 263 15214, M_{found} = 263 15205±0 00076 Separation of the enantiomers was carried out with HPLC on CHIRALCEL OD column, UV detection at 226 nm, eluent *n*-hexane/2-PrOH = 90/10 (v/v), flow

rate 1.0 ml/min., 5.38 min. (major isomer) and 8.04 min. (minor isomer)

2,3-Diphenyl-4-methyl-5,5-dimethoxy-isoxazolidine 18

M.p. 112 °C; 400 MHz ^{1}H NMR δ(ppm) 0.79 3H, d, J = 7.2 Hz, 4-CH_3; 2.85 1H, quintet, J = 7.2 Hz and J = 7.0 Hz, H-4; 3.25 3H, s, OCH_3; 3.41 3H, s, OCH_3; 4.96 1H, d, J = 7.0 Hz, H-3; 6.88 3H, m, ArH; 7.17 2H, m, ArH; 7.24-7.41 5H, m, ArH. ^{13}C NMR δ(ppm) 11.1 (4-CH_3), 45.4 (C-4), 49.4 (O-$\underline{C}H_3$), 51.2 (O-$\underline{C}H_3$), 72.5 (C-3), 114.8, 121.2, 121.4 (C-5), 127.3, 127.5, 128.4, 128.5, 138.3 (C_{ipso}), 151.4 (C_{ipso}). HRMS (rel. int.) = 300 (M^{+1}, 3), 299 (M^+, 19), 268 (16), 198 (18), 191 (94), 180 (31), 177 (19), 131 (4), 121 (13) 117 (15), 77 (100). The enantioselectivity of the reaction could not be determined with HPLC, because the enantiomers could not be separated by this technique using CHIRALCEL OB, OD or CHIRALPAK AD columns. The enantioselectivity was determined by HPLC analysis of the corresponding β-amino ester **21**.

2,3-Diphenyl-4-methyl-5,5-diethoxy-isoxazolidine 19

M.p. 93 °C; 400 MHz ^{1}H NMR δ(ppm) 0.78 3H, d, J = 7.2 Hz, 4-CH_3; 0.90 3H, t, J = 7.1 Hz, CH_3; 1.29 3H, t, J = 7.1 Hz, CH_3; 2.84 1H, quintet, J = 7.1 Hz and J = 6.9 Hz, H-4; 3.54-3.74 4H, m, 2x O-CH_2; 4.99 1H, d, J = 6.9 Hz, H-3; 6.87 3H, m, ArH; 7.16 2H, m, ArH; 7.31 3H, m, ArH; 7.41 2H, m, ArH. ^{13}C NMR δ(ppm) 11.1 (4-CH_3), 14.6 (CH_3), 15.0 (CH_3), 46.0 (C-4), 57.3 (CH_2), 59.5 (CH_2), 72.3 (C-3), 114.7, 120.9 (C-5), 121.0, 127.3, 127.4, 128.3, 128.5, 138.5 (C_{ipso}), 151.5 (C_{ipso}). HRMS (rel. int.) m/e : 328 (M^{+1}, 7), 327 (M^+, 34), 282 (-OEt, 37), 226 (12), 219 (95), 208 (10), 180 (51), 145 (56), 135 (38), 130 (100). Peak Match: M_{calc} = 327.1834, M_{found} = 327.18337 ±0.00096. $C_{20}H_{25}NO_3$ Calc. C 73.37, H 7.70, N 4.28 Found : C 73.36, H 7.70, N 4.34. The enantioselectivity was determined by HPLC using a CHIRALPAK AD column, UV detection at 254 nm, flow rate 0.75 ml/min., eluent *n*-hexane/2-PrOH = 98/2 (v/v), 9.53 min. (minor isomer) and 10.62 min. (major isomer) or at flow rate 1.0 ml/min., eluens *n*-hexane/2-PrOH = 99/1 (v/v), 10.10 min. (minor isomer) and 11.47 (major isomer).

***syn*-Methyl-3-anilino-2-methyl-3-phenylpropionate 21**[15a]

The *cis*-isoxazolidine **18** (200 mg, 0.67 mmol) was dissolved in 15 ml ethanol, 10% Pd(C) (ca. 100 mg) was added and the mixture was hydrogenated at room temperature under 1atm. H_2-pressure for 30 to 60 minutes under stirring. The reaction mixture was then filtered with a glass filter over a small amount of Celite, washed 2 times with 10 ml ethanol and concentrated under vacuum to yield the solid *syn*-β-amino ester **21** (174 mg, 96% yield). m.p. 98 °C (lit. 98-99 °C[15]); 400 MHz ^{1}H NMR δ(ppm) 1.55 3H, d, J = 7.1 Hz, 2-CH_3; 2.96 1H, quintet, J = 7.1 Hz and J = 5.0 Hz, H-2; 3.61 3H, s, OCH_3; 4.49 1H, broad s, NH (D_2O exchange); 4.72 1H, d, J = 5.0 Hz, H-3; 6.51 2H, d, J = 8.1 Hz, 2x ortho-N-ArH; 6.64 1H, t, J = 7.3 Hz, para-N-ArH; 7.07 2H, t, J = 7.3 and 8.1 Hz, 2x meta N-ArH; 7.22-7.31 5H, m, ArH. Doublet signal at 1.55 ppm (2-Me) and doublet at 4.72 ppm (H-3) become singlets after irradiation of H-2 resonance at 2.96 ppm. ^{13}C NMR δ(ppm) 11.8 (2-CH_3), 46.0 (C-2), 51.9 (O$\underline{C}H_3$), 59.6 (C-3), 113.6 (2x C_{ortho} N-Ar), 117.6 (C_{para} N-Ar), 126.8 (2x C_{meta} N-Ar), 127.3, 128.5, 129.0, 140.6 (C_{ipso}), 174.6 (C=O). The enantioselectivity of the

reaction was determined by HPLC using a CHIRALCEL OD column, UV detection at 250 nm, flow rate 1 0 ml/min , eluent *n*-hexane/2-PrOH = 99/1 (v/v)

4-Methyl-5,5-dimethoxy-isoxazolidine 22

Oil, 400 MHz ^{1}H-NMR δ (ppm) 1 30 3H, d, $J_{4CH3\ H4}$= 6 9 Hz, 4-CH_3, 2 66 1H, dq, $J_{H3,H4}$ = 9 9 Hz and $J_{H4,4CH3}$ = 6 9 Hz, H-4, 2 91 1H, dt, $J_{H12\ H12}$ = 12 1 Hz, $J_{H12,H13}$ = 4 1 Hz, $J_{H12\ H13}$ = 0 Hz, H-12, 3 00 1H, ddd, $J_{H12\ H13}$ = 5 1 Hz, $J_{H12\ H13}$ = 4 7 Hz, $J_{H12,H12}$ = 12 1 Hz, H-12', 3 31 3H, s, 5 -OCH_3, 3 35 1H, quintet, $J_{H13\ H12}$ = 0 Hz, $J_{H13,H12}$ = 4 7 Hz, $J_{H13,H13}$ = 11 1 Hz, H-13', 3 45 3H, s, 5-OCH_3, 3 49 1H, ddd, $J_{H13,H12}$ = 4 1 Hz, $J_{H13\ H12}$ = 5 1 Hz, $J_{H13,H13}$ = 11 1 Hz, H-13, 4 36 1H, d, $J_{H3,H4}$ = 9 9 Hz, H-3, 7 13 2H, m, H8 and H9, 7 19 2H, m, H7 and H10 ^{13}C NMR δ (ppm) 12 7 (4-Me), 28 0 (C-12), 47 1 (C-4), 49 4 (5-OMe'), 50 0 (C-13), 51 1 (5-OMe), 68 9 (C-3), 122 0 (C-5), 126 1 (C-9), 126 9 (C-10), 127 0 (C-8), 128 4 (C-7), 133 6 (C-11), 134 7 (C-6) HRMS (rel int) = 250 (M^{+1}, 2), 249 (M^+, 13), 218 (8) -OCH_3, 158 (13), 148 (68), 147 (28), 130 (34), 115 (9), 102 (100) Peak Match M_{calc}=249 13649, M_{found}=249 13657±0 00073 Separation of the enantiomers was achieved by HPLC on a CHIRALCEL OD column, UV detection at 254 nm, flow rate 1 0 ml/min , eluent *n* hexane/2 PrOH = 95/5 (v/v), 7 16 min (minor) and 9 55 min (major isomer)

4-Methyl-5,5-diethoxy-isoxazolidine 23

Oil, 400 MHz ^{1}H-NMR δ (ppm) 1 18 3H, t, J = 7 1 Hz, C$\underline{H}_3$-CH_2, 1 24 3H, t, J = 7 1 Hz, C$\underline{H}_3$ CH_2, 1 29 3H, d, $J_{4\ CH3\ H4}$= 6 9 Hz, 4-CH_3, 2 64 1H, dq, $J_{H3,H4}$ = 10 2 Hz en $J_{H4\ 4CH3}$ = 6 9 Hz, H-4, 2 88 1H, m, H-12, 2 98 1H, m, H-12', 3 37 1H, m, H-13 , 3 49 1H, m, H 13, 3 58 2H, q, J = 7 1 Hz, OC$\underline{H}_2$-CH_3, 3 74 1H, dq, H_A diastereotope OC$\underline{H}_2$-CH_3, 3 81 1H, dq, H_B diastereotope OC$\underline{H}_2$-CH_3, 4 35 1H, d, $J_{H3\ H4}$ = 10 2 Hz, H-3, 7 13 2H, m, H8 and H9, 7 18 2H, m, H7 and H10 ^{13}C NMR δ (ppm) 12 5 (4-Me), 15 3 (2x Me), 28 3 (C-12), 47 7 (C-4), 50 1 (C-13), 57 5 (OCH_2), 58 9 (OCH_2), 69 0 (C-3), 122 2 (C-5), 126 0 (C-9), 126 9 (C-10, C-8), 128 4 (C-7), 133 6 (C-11), 134 8 (C-6) HRMS (rel int) = 278 (M^{+1}, 1), 277 (M^+, 5), 232 (-OEt, 12), 204 (3), 158 (13), 148 (23), 131 (14), 130 (100), Peak Match M_{calc}= 277 3658, M_{fnd}= 277 3657 The separation of enantiomers was achieved by HPLC using a CHIRALCEL OD column, flow rate 0 75 ml/min , eluent *n*-hexane/2-PrOH = 95/5 (v/v), 7 07 min (major isomer) and 9 01 min (minor isomer)

4-Methyl-5,5-di-n-propoxy-isoxazolidine 24

Oil, 400 MHz ^{1}H-NMR δ (ppm) 0 90 3H, t, J = 7 4 Hz, C$\underline{H}_3$-CH_2, 0 96 3H, t, J = 7 1 Hz, C$\underline{H}_3$ CH_2,1 28 3H, d, $J_{4CH3,H4}$= 6 8 Hz, 4-CH_3, 1 61 4H, m, 2x CH_2-C$\underline{H}_2$-CH_3, 2 65 1H, dq, $J_{H3\ H4}$ = 10 3 Hz en $J_{H4,4CH3}$ = 6 8 Hz, H-4, 2 87 1H, m, H-12, 3 00 1H, m, H-12', 3 37 1H, m, H-13 , 3 44-3 50 3H, m, H-13 and OC$\underline{H}_2$-CH_2, 3 62 1H, dq, H_A diastereotope OC$\underline{H}_2$ CH_3, 3 72 1H, dq, H_B diastereotope OC$\underline{H}_2$-CH_3, 4 35 1H, d, $J_{H3,H4}$ = 10 3 Hz, H-3, 7 13 2H, m, H8 and H9, 7 18 2H, m, H7 and H10 ^{13}C NMR δ (ppm) 10 7 (2x Me), 12 5 (4-Me), 23 0 (CH_2), 23 1 (CH_2), 28 4 (C-12), 47 5 (C-4), 50 1 (C-13), 63 3 (5-OCH_2), 65 0 (5-OCH_2), 69 0 (C-3), 122 2 (C-5), 126 0 (C-9), 126 9 (C-8, C 10), 128 4 (C-7), 133 6 (C-11), 134 8 (C-6) HRMS (rel int) m/e 306 (M^{+1}, 3),

305 (M^+ 17), 246 (-*i*-PrO, 50), 186 (-*i*PrO, 7), 158 (100), 130 (61) Peak Match $C_{18}H_{27}NO_3$ M_{calc} = 305 1991, M_{found} = 305 19925 ± 0 00091

2,3-Diphenyl-4-methyl-5,5-di-isopropoxy-isoxazolidine 26

After purification by silica gel column chromatography with ether/hexane (1 2, v/v) as eluent the *cis*-isoxazolidine **26** was isolated as an oil 400 MHz ^{1}H NMR δ (ppm) 0 70 3H, d, J = 7 2 Hz, 4 CH_3, 1 02 3H, d, J = 6 3 Hz, CH_3, 1 27 6H, t, J = 6 3 Hz, 2x CH_3, 1 33 3H, d, J = 6 3 Hz, CH_3, 2 88 1H, dq, J = 7 2 Hz and J = 9 6 Hz, H-4, 4 14 1H, m, J = 6 3 Hz, $Me_2C(O)$-H, 4 54 1H, m, J = 6 3 Hz, $Me_2C(O)$-H, 4 73 1H, d, J = 9 6 Hz, H-3, 6 86 3H, m, N-ArH, 7 16 2H, m, N-ArH, 7 27 1H, m, ArH, 7 34 2H, m, ArH, 7 45 2H, m, ArH ^{13}C NMR δ (ppm) 10 9 (4-CH_3), 23 6 (Me), 23 9 (Me), 24 3 (2x Me), 45 4 (C-4), 66 0 (O-CMe_2), 66 1 (O-CMe_2), 72 3 (C-3), 114 6, 120 1 (C 5), 120 9, 127 4, 128 1, 128 2, 128 5, 139 2 (C_{ipso}), 150 9 (C_{ipso})

4-Ethyl-5,5-dioxolano-isoxazolidine 29

Oil, 400 MHz ^{1}H NMR δ (ppm) 0 95 3H, t, J =7 3 Hz, CH_3, 1 40 2H, m, J = 7 3 Hz, CH_2, 2 90 1H, ddd, $J_{H4\,H3}$ = 8 2 Hz, and J = 8 5 Hz, J = 5 9 Hz, H-4, 2 99 2H, m, H-12, 3 51 2H, m, H-13, 3 94 2H, t, J = 6 3 Hz, OCH_2, 4 11 2H, t, J = 6 3 Hz, OCH_2, 4 94 1H, d, $J_{H3,H4}$ = 8 2 Hz, H-3, 7 16 4H, m, ArH ^{13}C NMR δ(ppm) 13 4 (C-15), 20 4 (C-14), 26 1 (C-12), 50 5 (C-13), 51 8 (C-4), 64 6 (C-3), 64 7 (C 16, C-17), 125 8-128 7 (C-Ar and C-5), 132 7 (C-11), 135 5 (C-6) HRMS (rel int) m/e 262 (M^{+1}, 1), 261 (M^+, 1), 203 (6), 147 (24), 130 (37), 115 (62), 99 (100) Peak Match M_{calc} = 261 13649, M_{found} = 261 13639 ± 0 00076 The enantioselectivity of the reaction could not be determined by HPLC analysis using chiral columns

5,5-Dimethoxy-4-methyl-3-phenyl-N-methyl isoxazolidine 30 and 31

Oil, 400 MHz ^{1}H NMR δ(ppm) 0 76 1 5H, d, $J_{4\,CH3\,H4}$ = 7 3 Hz, 4-CH_3, 0 97 1 5H, d, $J_{4\text{-}CH3\,H4}$ = 6 9 Hz, 4-CH_3, 2 63 1 5H, s, N-CH_3, 2 70 1H, dq, J=7 3 Hz, H-4, 2 73 1 5H, s, N-CH_3, 3 36 1 5H, s, 5-OCH_3, 3 37 1 5H, s, 5-OCH_3, 3 38 0 5H, H-3, 3 40 1 5H, s, 5-OCH_3 , 3 43 1 5H, s, 5-OCH_3', 4 17 1 5H, d, J=6 7 Hz, H-3, 7 31 5H, m, ArH ^{13}C NMR δ(ppm) 10 7 (4-CH_3 endo and exo), 44 3 (C-4), 45 1 (C-4), 46 6 (N-CH_3), 49 2 (5-OCH_3), 49 6 (5-OCH_3'), 50 2 (N-CH_3), 50 4 (5-OCH_3), 50 8 (5-OCH_3), 75 6 (C-3), 80 3 (C-3), 119 0 (C-5), 121 0 (C-5), 127 5 (C-Ar), 127 9 (C-Ar), 128 0 (C-Ar), 128 2 (C-Ar), 128 6 (C-Ar), 136 6 (C-6), 137 6 (C-6) HRMS (rel int) m/e *endo* -**30** 238 (M^+ +1, 3 3), 237 (M^+, 21 9), 206 (-OCH_3, 38 5), 192 (11 2), 191 (-CH_3, 83 4) , 178 (2 7), 177 (23 9), 150 (29 6), 136 (59 1), 102 (100 0) HRMS (rel int) *exo* -**31** 238 (M^+ +1, 1) , 237 (M^+, 10), 206 (24), 192 (3), 191 (21), 178 (1), 177 (11), 150 (14), 136 (47), 102 (100) It was not possible to determine the enantioselectivity of the reaction by HPLC analysis

5,5-Dimethoxy-4-methyl-3-phenyl-N-benzyl isoxazolidine 33

This compound is not stable on silica gel and its purification by chromatography on this support gives in low yield an oil The hydrogenolysis of the crude isoxazolidine **33** gives the corresponding β-amino ester **34** in high yields (*vide infra*) 400 MHz ^{1}H NMR δ (ppm) 0 78 3H, $J_{4CH3\,H3}$=7 29

Hz, 4-CH_3, 2 73 1H, dq, $J_{H4\ 4CH3}$=7 18 Hz, $J_{H4,H3}$=6 90 Hz, H-4, 3 28 3H, s, 5-OCH_3, 3 36 3H, s, 5 OCH_3, 3 88 1H, d, J_{gem}=14 4 Hz, H-6a, 4 02 1H, d, J_{gem}=14 4 Hz, H-6b, 4 45 1H, d, $J_{H3\ H4}$=6 9 Hz, H-3, 7 31 10H, m, H-arom ^{13}C NMR δ(ppm) 10 8 (4-CH_3), 46 0 (C-4), 49 5 (5-OCH_3), 50 5 (5-OCH_3), 61 9 (Ph$\underline{C}H_2$), 73 3 (C-3), 121 0 (C-5), 127 0 (C-Ar), 127 2 (C-Ar), 127 5 (C Ar), 127 9 (C-Ar), 128 1 (C-Ar), 128 2 (C-Ar), 128 3 (C-Ar), 128 6 (C-Ar), 129 0 (C-Ar), 129 3 (C Ar), 137 0 (C_{ipso}), 137 8 (C_{ipso}) HRMS (rel int) m/e 314 (M^++1, 2), 313 (M^+, 10), 282 (-OCH_3, 2), 267 (-CH_3, 2), 226 (2), 213 (6), 212 (40), 194 (5), 191 (16), 149 (16), 121 (25), 102 (51), 91 (100) Peak Match M_{calc} = 313 1678, M_{found} = 313 1672 ± 0 0009 The enantioselectivity was determined by HPLC analysis of the corresponding β-amino ester **34**

Methyl (2R,3R)-3-amino-2-methyl-3-phenylpropionate 34[19]

To a solution of the crude isoxazolidine **33** (313 mg, 1 mmol) in methanol-water-acetic acid (20 2 1, v/v, 10 ml) was added $Pd(OH)_2$-carbon (Pearlman s catalyst[18], 250 mg) and the resultant black suspension was stirred under a hydrogen balloon for 5 hrs The reaction mixture was filtered through a plug of Celite and washed with methanol The filtrate was concentrated to give a white residue This residue was dissolved in sat aqueous $NaHCO_3$ and the solution was subsequently extracted with dichloromethane The combined organic extracts were dried ($MgSO_4$), filtered and evaporated to afford the free amino ester (2R,3R)-**34** (175 mg, 90% yield) The absolute configuration was established from the fact that the product has a negative optical rotation The enantiomer (2S,3S)-**34** has a positive rotation $[\alpha]_D^{25}$ = +15 8 (c 1 00, $CHCl_3$)[19a] 400 MHz ^1H NMR δ (ppm) 1 16 3H, d, J = 7 1 Hz, 2-CH_3, 1 68 2H, br s, NH_2, 2 76 1H, dq, J = 5 9 and 7 1 Hz, H 2, 3 58 3H, s, OCH_3, 4 29 1H, d, J = 5 9 Hz, H-3, 7 24 1H, m, *para*-ArH, 7 26 7 32 4H, m, ArH ^{13}C NMR δ(ppm) 11 9 (2-CH_3), 47 2 (C-2), 51 5 (OCH_3), 57 3 (C-3), 126 5, 127 2, 128 3 (Ar C), 143 6 (C_{ipso}), 175 4 (C=O) HRMS (rel int) m/e 193 (M^+, 0 3), 178 (-CH_3, 7), 177 (55), 158 (2), 145 (3), 132 (4), 122 (8), 121 (100), 105 (10) Peak Match $C_{11}H_{15}NO_2$ M_{calc} = 193 1103, M_{found} = 193 11021 ± 0 00097 The enantioselectivity of the reaction was determined by HPLC on a chiral Daicel HPLC column, type CHIRALCEL OD, UV detection at 226 nm, eluent *n* hexane/2-PrOH = 99/1 (v/v), flow rate 1 0 ml/min , (2R,3R)-**34** 22 2 min , (2S,3S)-**34** 36 0 min The enantioselectivity was also determined by NMR-analysis of the derivatized Mosher amide **35** The β-amino ester (2S,3S)-**34** (HPLC 57% ee) was dissolved in dichloromethane and (*R*)-Mosher acid chloride was added[20] After stirring at room temperature for 2 hrs the crude mixture was separated by flash chromatography on silica gel to afford the pure Mosher amide **35** as a mixture of two diastereomers Oil, 400 MHz ^1H NMR δ (ppm) 1 11 0 64H, d, J = 7 1 Hz, 2-CH_3 (2R,3R), 1 17 2 36H, d, J = 7 1 Hz, 2-CH_3 (2S,3S), 3 02 1H, m, H-2, 3 38 0 64H, s, OMe, 3 47 2 36H, s, OMe (2S,3S), 3 56 0 64H, s, OMe, 3 60 2 36H, s, OMe (2S,3S), 5 32 1H, m, H 3, 7 13 1H, m, NH, 7 23-7 43 10H, m, ArH ^{13}C NMR δ (ppm) 12 8 (2-Me, (2R,3R)), 13 1 (2-Me, (2S,3S)), 44 4 (C-2, (2R,3R), 44 5 (C-2, (2S,3S)), 51 9 (OMe), 55 0 and 55 1 (OMe), 77 2, 122 3, 125 1, 126 7, 126 9, 127 5, 127 6, 127 8, 128 4, 128 5, 129 4, 129 8, 132 4, 138 6 (Ar-C), 165 5 (C=O), 173 9 (C=O) ^{19}F-NMR δ (ppm) 11 00 s, CF_3 and 11 04 s, CF_3 (2S,3S) The resolution of the ^{19}F NMR spectrum was not good enough to give reliable integration HRMS (rel int) m/e

410 (M^{+1}, 0 3), 378 (-OMe, 2), 322 (10), 220 (20), 189 (32), 177 (55), 145 (3), 132 (3), 121 (100) Peak Match $C_{21}H_{22}NO_4F_3$ M_{calc} = 409 1500, M_{found} = 409 1501 ± 0 001

3.5 References and Notes

† Partially taken from Seerden, J -P G , Scholte op Reimer, A W A , Scheeren, J W *Tetrahedron Lett* **1994**, *35*, 4419-4422 This work was presented at IKCOC-6, november 7-11, 1994, Kyoto, Japan, abstracts OP-33 and PP-092

1 a) Tufariello, J J In *1,3-Dipolar Cycloadditions Chemistry*, Padwa, A , Ed , Wiley, New York, **1984**, vol 2, pp 83-168, b) Confalone, P N , Huie, E M *Org React* **1988**, *36*, 1-173, c) Balasubramanian, N *Org Prep Proc Int* **1985**, 25, d) Black, D S , Crozier, R F , Davis, V C *Synthesis*, **1975**, 205-221, e) Annunziata, R , Cinquini, M , Cozzi, F , Raimondi, L *Gazz Chim Ital* **1989**, *119*, 253-269, f) Mulzer, J *Nachr Chem Tech Lab* **1984**, *32*, 882-887, g) Torssell, K B G *Nitrile Oxides, Nitrones, and Nitronates in Organic Synthesis*, VCH Weinheim, **1988**, pp 1-47, 75-89, 129-327, h) Dopp, D , Dopp, H in "Houben-Weyl Methoden der Organischen Chemie , vol E14b, Klamann, D , Hagemann, H , Eds , Georg Thieme Verlag Stuttgart, **1990**, i) Grunanger, P , Vita-Finzi, P in *'The Chemistry of Heterocyclic Compounds'*, Taylor, E C , Ed , Vol 49, part 1, Chapter 3 'Isoxazolidines', John Wiley & Sons, New York, **1991**, pp 649-777

2 a) Murahashi, S -I , Imada, Y , Kohno, M , Kawakami, T *Synlett*, **1993**, 395-396 (ref 2 and 3 cited therein), b) Mukai, C , Kim, I J , Cho, W J , Kido, M , Hanaoka, M *J Chem Soc Perkin Ttrans 1* **1993**, 2495-2503, c) Murahashi, S -I , Sun, J , Tsuda, T *Tetrahedron Lett* **1993**, *34*, 2645 2648, d) Goti, A , Cicchi, S , Brandi, A , Pietrusiewitz, K M *Tetrahedron Asymmetry* **1991**, *2*, 1371-1378, e) Takahashi, T , Fujii, A , Sugita, J , Hagi, T , Kitano, K , Arai, Y , Koizumi, T , Shiro, M *Tetrahedron Asymmetry* **1991**, *2*, 1379-1390, f) Brandi, A , Cicchi, S , Goti, A , Koprowski, M , Pietrusiewicz, K M *J Org Chem* **1994**, *59*, 1315-1318, g) Wovkulich, P M , Baggiolini, E G , Hennessy, B M , Uskokovic, M R *Heterocycles* **1993**, *35*, 791-797, h) Tamura, O , Yamaguchi, T , Noe, K , Sakamoto, M *Tetrahedron Lett* **1993**, *34*, 4009-4010, i) Tamura, O , Yamaguchi, T , Okabe, T , Sakamoto, M *Synlett* **1994**, 620-622, j) Konosu, T , Oida, S *Chem Pharm Bull* **1993**, *41*, 1012-1018, k) Keller, E , de Lange, B , Rispens, M T , Feringa, B L *Tetrahedron* **1993**, *49*, 8899-8910, Rispens, M T , Keller, E , de Lange, B , Zijlstra, R W J , Feringa, B L *Tetrahedron Asymmetry* **1994**, *5*, 607 624, l) Gravestock, M B , Knight, D W , Lovell, J S , Thornton, S R *J Chem Soc Perkin Trans 1* **1994**, 1661-1663, m) Saito, S , Ishikawa, T , Moriwake, T *J Org Chem* **1994**, *59*, 4375-4377, n) Naito, T , Ikai, M , Shirakawa, M , Fujimoto, K , Ninomiya, I , Kiguchi, T *J Chem Soc Perkin Trans 1* **1994**, 773-775, o) Aurich, H G , Quintero, J -L R *Tetrahedron* **1994**, *50*, 3929-3942, p) Ishizuka, T , Matsunaga, H , Iwashita, J , Arai, T , Kunieda, T *Heterocycles* **1994**, *37*, 715-718, q) Oppolzer, W , Deerberg, J , Tamura, O *Helv Chim Acta* **1994**, *77*, 554-560

3 a) Narasaka, K *Synthesis* **1991**, 1-11, b) Kagan, H B , Riant, O *Chem Rev* **1992**, 1007-

1019, c) Lohray, B B , Bhushan, V *Angew Chem* **1992**, *104*, 740-741, d) Wallbaum, S , Martens, J *Tetrahedron Asymmetry* **1992**, *3*, 1475-1504, e) Deloux, L , Srebnik, M *Chem Rev* **1993**, *93*, 763-784, f) for recent review on asymmetric reactions with chiral Lewis acid catalysts see Maruoka, K , Yamamoto, H in "Catalytic Asymmetric Synthesis' , Ojima, I , Ed , VCH Weinheim, **1993**, Chapter 9, p 413-440

4 Kanemasa, S , Uemura, T , Wada, E *Tetrahedron Lett* **1992**, *33*, 7889-7892, Kanemasa, S , Tsuruoka, T , Wada, E *Tetrahedron Lett* **1993**, *34*, 87-90

5 Chiral oxazaborolidines derived from N-sulphonylated amino acids have been used in several asymmetric organic reactions, see a) Seerden, J -P G , Scheeren, J W *Tetrahedron Lett* **1993**, *34*, 2669-2672, b) Seerden, J P G , Scholte op Reimer, A W A , Scheeren, J W *Tetrahedron Lett* **1994**, *35*, 4419-4422, c) for reviews, see ref 3c and 3e

6 The sulphonamides were prepared from commercially available amino acids and derivatives according to a procedure described in Houben-Weyl, *'Methoden der Organischen Chemie'*, Band 15/1, *Synthese von Peptiden* I, 4^{e}Auflage, Georg Thieme Verlag, Stuttgart, **1974**, pp 223-233 Under these conditions no racemisation of the sulphonamides occurs

7 For the preparation of nitrones via oxidation of secondary amines, see Murahashi, S I , Shiota, T , Imada, Y *Org Synth Vol 70*, **1992**, 265-271, Murahashi, S -I , Mitsui, H , Watanabe, T , Zenki, S -i *Tetrahedron Lett* **1983**, *24*, 1049-1052

8 For examples of 1,3-dipolar cycloaddition reactions of nitrones with ketene O,O-dialkyl acetals, see a) Scarpati, R , Sica, D , Santacroce, C *Gazz Chim Ital* **1966**, *96*, 375-386, b) Huisgen, R , Grashey, R , Seidl, H , Hauck, H *Chem Ber* **1968**, *101*, 2559-2563, c) chiral nitrone with cyclic ketene acetal Keirs, D , Moffat, D , Overton, K , Tomanek, R *J Chem Soc Perkin Trans I* **1991**, 1041 1051, d) achiral nitrone with cyclic ketene acetals under microwave irradiation and solvent-free conditions Díaz Ortiz, A , Diez-Barra, E , de la Hoz, A , Prieto, P , Moreno, A *J Chem Soc Perkin Trans I* **1994**, 3595-3598

9 Silyl ketene acetals are known to give silyl group-transfer 1,3-addition reactions with nitrones instead of ordinary 1,3-dipolar cycloadditions Tomoda, S , Takeuchi, Y , Nomura, Y *Chem Lett* **1982**, 1787-1790, Kita, Y , Itoh, F , Tamura, O , Ke, Y Y , Tamura, Y *Tetrahedron Lett* **1987**, *28*, 1431-1434, Kita, Y , Tamura, O , Itoh, F , Kishino, H , Miki, T , Kohno, M , Tamura, Y *J Chem Soc , Chem Commun* **1988**, 761-763

10 For examples of 1,3-dipolar cycloaddition of nitrones with enol ethers, see a) Dicken, C M , DeShong, P *J Org Chem* **1982**, *47*, 2047-2051, Dicken, C M , DeShong, P , Staib, R R , Freyer, A J , Weinreb, S M *J Org Chem* **1982**, *47*, 4397, b) application in amino sugar synthesis DeShong, P , Leginus, J M *J Am Chem Soc* **1983**, *105*, 1686-1688, DeShong, P , Dicken, C M , Leginus, J M , Whittle, R R *J Am Chem Soc* **1984**, *106*, 5598-5602, c) Iwashita, T , Kusumi, T , Kakisawa, H *Chem Lett* **1979**, 1337-1340, Iwashita, T , Kusumi, T , Kakisawa, H *J Org Chem* **1982**, *47*, 230-233, d) Huisgen, R , Grashey, R , Seidl, H , Hauck, H *Chem Ber* **1968**, *101*, 2559-2567, e) Bravo, P , Bruché, L , Farina, A , Fronza, G , Meille, S V , Merli, A *Tetrahedron Asymmetry* **1993**, *4*, 2131-2134

11 The corresponding silyl enol ethers are reported to give a regioselective TMSOTf-catalyzed

[3+2]-cycloaddition with nitrones affording 5-silyloxyisoxazolidines with poor *endo/exo* stereoselectivity Dhavale, D D , Trombini, C *J Chem Soc , Chem Commun* **1992**, 1268-1270, Camiletti, C , Dhavale, D D , Gentilucci, L , Trombini, C *J Chem Soc Perkin Trans I* **1993**, 3157-3165, Camiletti, C , Poletti, L , Trombini, C *J Org Chem* **1994**, *59*, 6843-6846 Preliminary results on the 1,3-dipolar cycloaddition of several nitrones with enol ethers show that this reaction is strongly catalyzed by chiral oxazaborolidines at room temperature yielding 5-alkoxy-isoxazolidines in high yield (Chapter 5, to be published)

12 Scheeren, J W , Aben, R W M , Ooms, H J , Nivard, R J F *J Org Chem* **1977**, *42*, 3128-3132, J W Scheeren, "Keten-O,O-acetale" in Houben-Weyl, 'Methoden der Organischen Chemie', H Kropf, E Schaumann (Eds), Georg Thieme Verlag, Stuttgart, **1993**, Band E15, 1674-1736

13 This ligand has been succesfully applied in catalytic asymmetric allylation reactions Ishihara, K , Mouri, M , Gao, Q , Maruyama, T , Furuta, K , Yamamoto, H *J Am Chem Soc* **1993**, *115*, 11490-11495

14 At that stage of our investigations the important role of the solvent on the enantioselectivity (see Chapter 4) was not taken into consideration The catalyst preparation method starting from 1M BH_3-THF in THF introduces *ca* 12 eq THF to the reaction mixture The literature procedures for catalyst preparation starting from alkyl- or arylboronic acids usually require the polar solvent propionitrile for reasons of better solvation, see for example ref 3c, 3e and ref 13 The presence of 4Å molecular sieves during catalyst preparation is necessary to remove the water

15 a) preparation of *syn-* and *anti*-β-amino ester, m p 98-99 °C resp 83-84 °C Luche, J L , Kagan, H B *Bull Soc Chim France* **1969**, 3500-3505, b) Barluenga, J , Fananas, F J , Yus, M *J Org Chem* **1979**, *44*, 4798-4801, c) Guanti, G , Narisano, E , Banfi, L *Tetrahedron Lett* **1987**, *28*, 4331-4334, d) Ojima, I , Inaba, S -i , Yoshida, K *Tetrahedron Lett* **1977**, 3643-3646

16 Aben, R W M , Scheeren, J W *Recl Trav Chim Pays-Bas* **1990**, *109*, 399

17 General procedures for the synthesis of N-benzyl nitrones are a) catalytic oxidation of secondary amines ref 10 , b) reaction of carbonyl compounds with hydroxylamines Dondoni, A , Franco, S , Junquera, F , Merchan, F , Merino, P , Tejero, T *Synth Commun* **1994**, *24*, 2537 2550, c) catalytic oxidation of *N,N*-disubstituted hydroxylamines with NMO/TPAP Goti, A , De Sarlo, F , Romani, M *Tetrahedron Lett* **1994**, *35*, 6571-6574, c)

18 Pearlman, W M *Tetrahedron Lett* **1967**, *17*, 1663

19 a) Davies, S G , Garrido, N M , Ichihara, O , Walters, I A S *J Chem Soc , Chem Commun* **1993**, 1153-1155, b) Davies, S G , Ichihara, O , Walters, I A S *J Chem Soc , Perkin Trans I* **1994**, 1141-1147, c) Preparation of corresponding trans-**34** see Davies, S G , Walters, I A S *J Chem Soc , Perkin Trans I* **1994**, 1129-1139

20 Dale, J A , Mosher, H S *J Am Chem Soc* **1973**, *95*, 512, for a review on the determination of enantiomeric purity by NMR, see Parker, D *Chem Rev* **1991**, *91*, 1441-1457

21 Bjørgo, J , Boyd, D R , Neill, D C , Jennings, W B *J Chem Soc , Perkin I* **1977**, 254

22 The Z-geometry of C,N-diphenylnitrone is discussed in a) Koyano, K , Suzuki, H *Tetrahedron Lett* **1968**, 1859, b) Koyano, K , Suzuki, H *Bull Chem Soc Jpn* **1969**, *42*, 3306, c) For the *E*-geometry of C,N-diphenylnitrone see Bravo, P , Bruché, L , Farina, A , Fronza, G , Meille, S V , Merli, A *Tetrahedron Asymmetry* **1993**, *4*, 2131-2134

23 For the preparation of BF_3-nitrone complexes, see a) Zeeh, B *Synthesis*, **1968**, 37, b) Minkin, V I , Medyantseva, E A , Andreeva, I M , Yureva, V A *Zhur Org Khim* **1974**, *10*, 2597

24 See for reactions of ketene acetals with aldehydes Hofstraat, R G , Scheeren, H W , Nivard, R J F *J Chem Soc , Perkin Trans I* **1985**, 561, Hofstraat, R G *Thesis*, University of Nijmegen, **1987**, and for reactions with imines Aben, R W M , Smit, R , Scheeren, J W *J Org Chem* , **1987**, *52*, 365-370 For a review on the chemistry of ketene acetals see Scheeren, J W *Recl Trav Chim Pays-Bas* **1986**, *105*, 71-84, see also ref 12

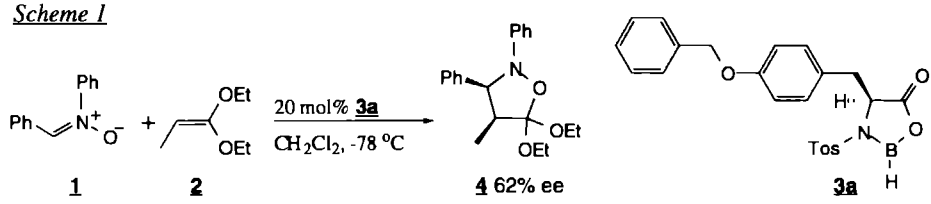
CHAPTER 4

Dramatic Solvent Effects on the Enantioselectivity of Asymmetric 1,3-Dipolar Cycloaddition Reactions of Nitrones with Ketene Acetals Catalyzed by Chiral Oxazaborolidines†

4.1 Introduction

The asymmetric 1,3-dipolar cycloaddition of nitrones is a key reaction in the synthesis of various biologically active compounds[1]. Moderate to good chiral induction has been achieved with chiral nitrones or chiral dipolarophiles[2]. In Chapter 3 of this thesis the first examples of catalytic asymmetric 1,3-dipolar cycloadditions of nitrones (e.g. C,N-diphenylnitrone **1**) with ketene acetals (e.g. 1,1-diethoxypropene **2**) catalyzed by chiral oxazaborolidines **3** were reported (*Scheme 1*)[3].

Scheme 1



1 **2** **4** 62% ee **3a**

The chiral Lewis acid activates the nitrone by complexing the oxygen atom of the nitrone and lowering the LUMO energy. The electron-rich ketene O,O-dialkyl acetals are expected to give a HOMO(alkene)-LUMO(nitrone) controlled 1,3-dipolar cycloaddition. The regio- and stereoselective formation of *cis*-5,5-dialkoxy-isoxazolidine cycloadduct can be explained via the less sterically hindered transoid approach of the ketene acetal to the nitrone and the formation of a dipolar intermediate[4]. The enantioselectivity appeared to be determined by the position of a phenyl group in the side-chain substituent of the chiral ligand. Analogous results were found for the chiral oxazaborolidine catalyzed Diels-Alder reaction of α,β-enals with simple dienes[5]. Considerable enhancement of enantioselectivity (up to 62% ee of (-)-**4**[5]) was achieved with *L*-tyrosine(O-benzyl ether)-derived oxazaborolidine **3a**. Attractive donor-acceptor interactions[5,6] between the side-chain substituent of **3a** and the electron-poor C-phenyl part of the nitrone are believed to determine the

enantioselectivity Systematic structural variation of the chiral catalyst and reactants is obviously the first step in fine-tuning the enantioselectivity[7]

In order to optimize the enantioselectivity and to gain more insight in the chiral recognition mechanism the effect of the starting borane in the catalyst preparation, the effect of chiral oxazaborolidines derived from amino acids with sterically demanding side-chains, and the influence of various polar and polarizable solvents on the enantioselectivity were investigated In addition, the chiral oxazaborolidine catalyzed 1,3-dipolar cycloaddition of C-phenyl-N-benzyl nitrone was further studied, in view of the potential application of the cycloadducts in the synthesis of chiral β-amino esters

4.2 Results and discussion

4.2.1 Catalytic asymmetric 1,3-dipolar cycloaddition of C-phenyl-N-phenyl nitrone

Reaction parameters

Before investigating other chiral oxazaborolidines we first optimized some reaction parameters that might influence the enantioselectivity In the standard procedure for 1,3-dipolar cycloaddition 3 equivalents of ketene acetal, 20 mol% of chiral catalyst and a reaction temperature of -78 °C were used (*Scheme 1*) It was found that the reaction can be performed with 1 5 equivalents of ketene acetal in the presence of 10 mol% of chiral oxazaborolidine **3a** at -78 °C without any loss of reactivity, regio-, stereo- or enantioselectivity The enantioselectivity decreases at higher temperatures (from 62% ee at -78 °C to 32% ee at room temperature), according to the thermodynamics associated with asymmetric synthesis (see Chapter 1)

Sterically demanding side chain substituents

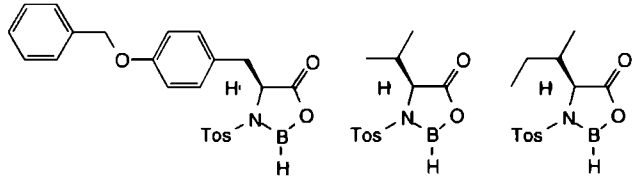
Chiral oxazaborolidines **3b** and **3c**, derived from *L*-α-amino acids[8] with sterically demanding side-chain substituents (*L*-valine and *L*-isoleucine, respectively) and BH_3 THF gave dramaticly lower enantioselectivities than **3a** (Table 1) Again, these results provide evidence that attractive donor-acceptor interactions between the side-chain substituent and the nitrone probably control the enantioselectivity when using chiral oxazaborolidine **3a**

Influence of starting borane

The *in situ* preparation of a chiral oxazaborolidine catalyst usually starts by adding an equimolar amount of commercially available BH_3-THF complex, as a 1M solution in THF, to a suspension of the crystalline N-tosyl-*L*-α-amino acid in dichloromethane, which is the standard solvent for Lewis acid catalyzed reactions However, this preparation method introduces *ca* 12 equiv of THF (from the BH_3-THF solution) in the reaction mixture To exclude the presence of donor solvents and to study the influence of THF, the oxazaborolidines **3a**, **3b** and **3c** were alsot prepared from commercially available BH_3-SMe_2 as a 1M solution in CH_2Cl_2 The 1,3-dipolar cycloaddition of nitrone **1** with ketene acetal **2** catalyzed by **3a** now gave a slight decrease in

enantioselectivity from 62% ee to 48% ee of (-)-**4** Very surprisingly, a dramatic reversal of enantioselectivity was observed with the valine and isoleucine-derived catalysts **3b** and **3c** The opposite enantiomer (+)-**4** was now obtained with 70 resp 73% ee (Table 1) In the absence of donor solvent THF the enantiofacial shielding of the nitrone caused by **3b** and **3c** must origin from steric hindrance by the sterically demanding isopropyl and isobutyl group

Table 1 Enantioselectivity in the asymmetric 1,3-dipolar cycloaddition of nitrone **1** and ketene acetal **2** catalyzed by oxazaborolidines **3**[a] (*Scheme 1*)

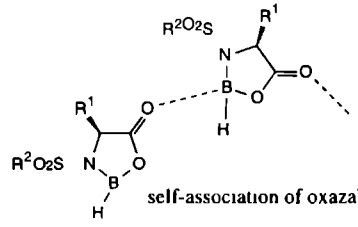


3a **3b** **3c**

starting borane	e e **4** (%)	e e **4** (%)	e e **4** (%)
BH_3 THF (+ 12 eq THF)	62 (-)	4 (-)	0
BH_3 SMe_2	48 (-)	70 (+)	73 (+)

[a]All reactions were run on the following scale 1 0 mmol nitrone with 10 mol% oxazaborolidine **3** (*in situ* prepared from 1M BH_3 THF in THF or 1M BH_3 SMe_2 in CH_2Cl_2) and 1 5 equiv ketene acetal in 4 ml CH_2Cl_2 at -78 °C

Helmchen *et al* [7a] found almost complete loss of enantioselectivity in the asymmetric Diels-Alder reaction of cyclopentadiene with α,β-enals when the catalyst **3b** was prepared from 1M BH_3-SMe_2 in dichloromethane In the acceptor solvent dichloromethane self-association of the catalyst *via* the carbonyl group is supposed to decrease the enantioselectivity by shielding the C_α-*Si* enal face When the oxazaborolidine catalysts are prepared from BH_3-THF (1M solution in THF) it is assumed that the oxazaborolidines are present as monomeric species



self-association of oxazaborolidines

From Table 1 it seems apparent that a donor solvent like THF does not interfere in the transition state of the chiral oxazaborolidine **3a** catalyzed 1,3-dipolar cycloaddition in which the enantioselectivity is determined by attractive π-π interactions This may indicate that in dichloromethane the self-association of oxazaborolidine **3a**, prepared from BH_3-SMe_2 in dichloromethane, does not take

place, or exerts a synergic effect in the enantioface discrimination The presence of THF has, however, a dramatic effect on the enantioselectivity when this selectivity is governed by steric hindrance in the transition state, as was suggested for oxazaborolidines **3b**[7a] and **3c** Possible self-association of the oxazaborolidines **3b** and **3c** is no loger possible, which decreases the selectivity The donor solvent THF might also be involved in selective solvation of the nitrone or the side-chain substituent in the transition state These results stimulated us to investigate in more detail whether specific solvent interactions with the nitrone or the side-chain substituent can control the enantioselectivity

Polar and polarizable solvents

To study the influence of the solvent composition on the enantioselectivity of the 1,3-dipolar cycloaddition of nitrone **1** to ketene acetal **2**, catalyzed by chiral oxazaborolidine **3a**, several polar and polarizable solvents[9,10] (Figure 1) were screened (Table 2) Special attention was paid to solvents having similar structural features as the aromatic side-chain substituent in **3a** in order to study possible competitive effects on π-π interactions All reactions were performed in dichloromethane as the standard solvent at -78 °C The chiral catalyst **3a** was prepared *in situ* from 1M BH_3 SMe_2 in dichloromethane at room temperature

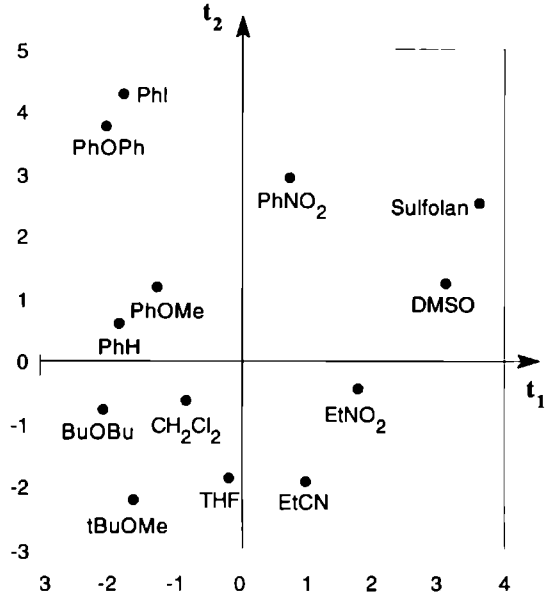


Figure 1 Plot of solvent polarity (t_1) vs solvent polarizability (t_2)[9] for various solvents

Very surprisingly, the presence of 2 5 vol% co-solvent in the reaction mixture had dramatic effects on the enantioselectivity[11] of the oxazaborolidine **3a** (prepared from 1M BH_3 SMe_2 in CH_2Cl_2) catalyzed cycloaddition as shown in Table 2 Except for benzene and THF[12], all co-solvents gave a reversal of enantioselectivity leading to the formation of (+)-**4** Optimization of the enantioselectivity

up to 79% ee of (+)-**4** was achieved by increasing the concentration of the cosolvent (Table 3) This solvent effect can not be rationally explained by a simple increase or decrease of the polarity or polarizability of the solvent mixture as apparent from Figure 1

Table 2 Influence of 2 5 vol% cosolvent on the enantioselectivity of the 1,3-dipolar cycloaddition of nitrone **1** and ketene acetal **2** catalyzed by **3a** in CH_2Cl_2[a]

cosolvent[b]	% ee **4**	cosolvent[b]	% ee **4**
-	48 (-)	THF	62 (-)
*t*BuOMe	26 (+)	EtCN	16 (+)
*n*BuO*n*Bu	14 (+)	$EtNO_2$	43 (+)
PhH	39 (-)	DMSO	6 (+)
PhOMe	4 (+)	Sulfolan	15 (+)
$PhCH_2OCH_2Ph$	33 (+)	$PhNO_2$	33 (+)
PhOPh	58 (+)	PhI	8 (+)

[a]Reactions were run on the following scale 1 0 mmol nitrone, 10 mol% oxazaborolidine **3a** (*in situ* prepared from 1M BH_3 SMe_2 in CH_2Cl_2), 1 5 eq ketene acetal in 4 ml solvent at -78 °C,[b] 0 1 ml (2 5 vol %) cosolvent

Table 3 Optimization of the solvent effect

cosolvent [a]	vol%	% ee **4**
$EtNO_2$	2.5	43 (+)
	1 0	**60 (+)**
	25	60 (+)
PhOPh	2 5	58 (+)
	10	72 (+)
	1 5	**79 (+)**
$PhCH_2OCH_2Ph$	2.5	33 (+)
	5	57 (+)
	7.5	**71 (+)**
	10	53 (+)

[a] Dichloromethane was used as solvent

Solvents of low polarity, e g *t*BuOMe and *n*BuO*n*Bu, gave the same effect as highly polar solvents, e.g DMSO and sulfolan The highly polarizable iodobenzene gave the same effect as the low polarizable *t*BuOMe or *n*BuO*n*Bu However, the striking structural similarities of diphenyl ether and dibenzyl ether with the side-chain substituent of **3a** suggest that reversal of enantioselectivity with these particular 'ligand-like" cosolvents[11c] origins from efficient solvation of the side-chain The solvated *p*-benzyloxybenzyl side-chain behaves as a bulky group to give the same enantioselectivity as found for sterically demanding catalysts **3b** and **3c** The effects of nitroethane, nitrobenzene

benzene and tetrahydrofuran in this reaction make clear that solvation of molecules in solvent mixtures is still very complicated and not easy to unravel. Self-association of the oxazaborolidine *via* its carbonyl oxygen atom may be more or less dependent on the solvent composition, which is reflected in the various enantioselectivities observed. Unfortunately, the absolute configuration of the cycloadduct **4** and its derivatives is unknown which makes it difficult to rationalize the results on the basis of a transition state model of the reaction.

The dramatic loss of enantioselectivity from 62% ee to 4% ee observed with a 3,5-bis(triflouromethyl)benzene substituent at the boron atom of oxazaborolidine **3a** in propionitril (Chapter 3) compared to the BH_3-THF derived oxazaborolidine in dichloromethane may also originate from a solvent effect instead of a substituent effect.

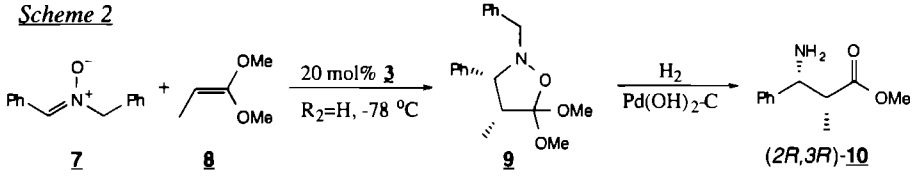
Recently, molecular dynamics simulations in combination with experimental CD spectroscopy has been used to probe the solvent structure around a chiral molecule[13d]. It was found that a chiral collective-structure in the solvent can be induced even when the solvent molecules are achiral. The magnitude of the effect appeared to depend on the nature of the solute as well as on the type of the solvent. The possible involvement of induced chiral solvent structures in the transition state makes a rationalization with simple transition state models more difficult.

4.2.2 Catalytic asymmetric 1,3-dipolar cycloaddition of C-phenyl-N-benzyl nitrone

The application of N-benzyl nitrones[14] in 1,3-dipolar cycloaddition reactions opens an interesting route to natural products because by simple debenzylation a primary amino function can be introduced in a molecule. The chiral oxazaborolidine catalyzed 1,3-dipolar cycloaddition of N-benzyl nitrones with ketene acetals followed by a catalytic cleavage of N-O bond and debenzylation provides a very mild and convenient asymmetric synthesis of β-amino esters in two catalytic steps (see Chapter 3)[3a,3e,15] From a mechanistic and synthetic point of view the change of a N-phenyl to a N-benzyl group in the nitrone is of interest and it may influence the enantioselectivity of the reaction. As was shown in Chapter 3, a possible donor-acceptor interaction of the side-chain substituent of **3a** with the N-aryl substituent of the catalyst is strongly dependent on the exact location of the donor and acceptor moieties.

The reaction of C-phenyl-N-benzyl nitrone **7** with ketene acetal **8** is strongly catalyzed by 20 mol% of chiral oxazaborolidines **3** derived from BH_3-THF and N-tosyl-*L*-amino acids in dichloromethane at -78 °C (*Scheme 2*, Table 3).

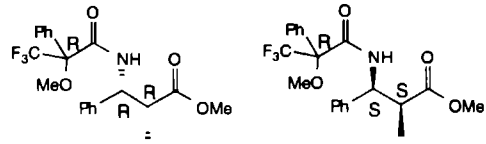
Scheme 2



7 **8** **9** (*2R,3R*)-**10**

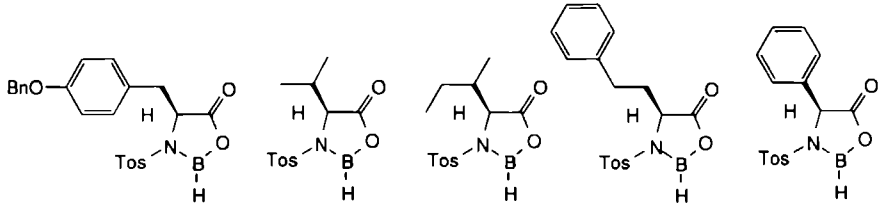
The corresponding *cis*-2-benzyl-3-phenyl-4-methyl-5,5-dimethoxy-isoxazolidine **9** was regio- and stereoselectively formed in a quantitative yield. The relative and absolute stereochemistry of **9** was established by converting the cycloadduct via hydrogenolysis in one step with hydrogen on $Pd(OH)_2$-

carbon (Pearlman's catalyst)[16] to the known (*2R,3R*)-β-amino ester **10**[17] The enantioselectivity was determined by chiral HPLC-analysis of the β-amino ester **10**, and by GC- and ^{1}H- and ^{19}F NMR analysis of the corresponding diastereomeric Mosher-amides



In order to optimize the enantioselectivity of the reaction and to gain further insight in its origin, several parameters were investigated which earlier were found to be important for the cycloaddition reaction of nitrone **1**, i e the starting borane solution, the side-chain substituent and the solvent Itt was observed that the use of 1 5 equivalents of ketene acetal **8** gave slow conversion of the nitrone **7** in contrast to nitrone **1** The use of 3 equivalents of the ketene acetal was necessary to obtain quantitative conversion of the nitrone after 16-24 hours at -78 °C Next, the influence of aliphatic side-chain substituents in the oxazaborolidines, *in situ* prepared from BH_3-SMe_2, were studied in THF-free solution (Table 4)

Table 4 Asymmetric 1,3-dipolar cycloaddition of nitrone **7** and ketene acetal **8** catalyzed by oxazaborolidines **3**[a]



catalyst	**3a**	**3b**	**3c**	**3d**	**3e**
starting borane	e e **10** (%)	e e **10** (%)	e e **10** (%)	e e **10** (%)	e e **10** (%)
BH_3-THF (+ 12 eq THF)	0	35 (*2R,3R*)	45 (*2R,3R*)	59 (*2R,3R*)	17 (*2R,3R*)
BH_3-SMe_2	8 (*2R,3R*)	47 (*2R,3R*)	39 (*2R,3R*)	11 (*2R,3R*)	10 (*2S,3S*)

[a]All reactions were run on the following scale 1 0 mmol nitrone 20 mol% of oxazaborolidine **3** (*in situ* prepared from 1M BH_3-THF in THF or 1M BH_3 SMe_2 in CH_2Cl_2) and 3 equiv ketene acetal in 4 ml solvent at 78 °C

The results in Table 4 show that, in contrast to nitrone **1**, the change of BH_3-THF to BH_3-SMe_2 has no effect on the enantioselectivity when the sterically demanding oxazaborolidines **3b** or **3c** with bulky aliphatic side chains are applied as catalysts If self-association of the catalysts **3b** or **3c** occurs, this association must have the same directional effect on the enantioselectivity as the steric hindrance exerted by the side-chain substituent This also implies that the orientation of N-phenyl nitrone **1** and N-benzyl nitrone **7** in the transition state must be quite different Considerable loss of

Re-face selectivity was observed when the type of starting borane was changed in the case of oxazaborolidines **3d** and **3e** The latter catalysts contain aromatic side-chain substituents Catalyst **3e** even gave a small reversal of enantioselectivity with preferential formation of the opposite enantiomer (*2S 3S*)-**10** The tyrosine(O-benzyl ether)-derived oxazaborolidine **3a** gave dramatically low enantioselectivities with nitrone **7**, when this catalyst was prepared from BH_3-THF or BH_3-SMe_2, in contrast to nitrone **1** where this catalyst gave the highest ee This poor enantioselectivity could be the result of a competition between attractive π-π- and repulsive steric interactions in the transition state

In the previous section (4 2 1) it was shown that for the chiral oxazaborolidine **3a**-catalyzed reaction of nitrone **1** the presence of "ligand-like" solvents (e g dibenzyl ether) gave dramatic reversals of enantioselectivity Likewise, the influence of co-solvents on the enantioselectivity of the asymmetric 1,3-dipolar cycloaddition of nitrone **7** catalyzed by various oxazaborolidines was studied (Table 5) The results of Table 5 show that oxazaborolidines **3a**, **3d** and **3e**, which have an aromatic side-chain substituent, give reversal of enantioselectivity in the presence of aromatic solvents, e g toluene, and lead to (*2S,3S*)-**10** For oxazaborolidine **3b**, which has an aliphatic side-chain substituent) *re*-face enantioselectivity is retained in the presence of toluene Optimization of the solvent effect gave up to 74% ee of (*2S,3S*)-**10** for the *L*-phenylglycine-derived oxazaborolidine **3e** and toluene as solvent (entry 13) No further increase of enantioselectivity was observed when catalyst **3e** was prepared from a commercially available 1M BH_3-SMe_2 solution in toluene (entry 14)

Table 5 Effect of co-solvents on the enantioselectivity of the 1,3-dipolar cycloaddition of nitrone **7** and ketene acetal **8** catalyzed by chiral oxazaborolidines **3**[a] prepared from 1M BH_3-SMe_2

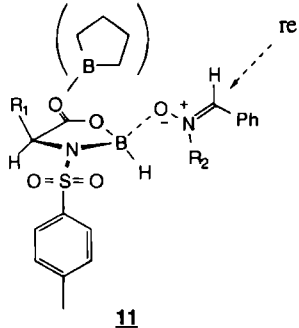
entry	catalyst	R	co-solvent[a]	vol%	e e (%) **10**
1	**3a**	4-($PhCH_2O$)-$PhCH_2$	-	-	8 (*2R,3R*)
2			$PhCH_3$	50	18 (*2S,3S*)
3			$PhCH_2OCH_2Ph$	2 5	34 (*2S,3S*)
4	**3b**	*i*-Pr	-	-	47 (*2R,3R*)
5			THF	100	21 (*2R,3R*)
6			$PhCH_3$	50	25 (*2R,3R*)
7	**3d**	$PhCH_2CH_2$	-	-	11 (*2R,3R*)
8			PhH	50	15 (*2S,3S*)
9	**3e**	Ph	-	-	10 (*2S,3S*)
10			$PhCH_2OCH_2Ph$	2.5	11 (*2S,3S*)
11			PhH	50	34 (*2S,3S*)
12			$PhCH_3$	50	40 (*2S,3S*)
13			$PhCH_3$	97 5	**74 (*2S,3S*)**
14			$PhCH_3$	100[b]	68 (*2S,3S*)

[a] Dichloromethane was used as solvent, the catalyst was prepared from BH_3 SMe_2 (1M in CH_2Cl_2), [b] The catalyst was prepared from BH_3-SMe_2 (1M in toluene) and the reaction was carried out in toluene as solvent

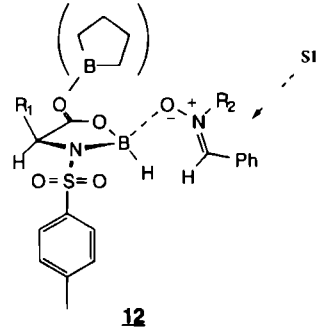
4.3 Working models

The results outlined above demonstrate that the ability to control the enantioselectivity of the cycloaddition reactions by using appropiate solvents seems to be rather general The observed enantioface selectivities can be visualized by working models **11** and **12** which are based on the following assumptions (i) the nitrone, in its *E*-configuration[20], is complexed to the boron via its oxygen atom, (ii) all substituents of the oxazaborolidine ring are positioned as far as possible from each other, (iii) the conformers **11** and **12**, obtained by rotation around the B-O, O-N and N-R_2 bonds of the *E*-nitrone part, are expected to be the more stable ones Solvents effects can be explained, in principle, by taking into account (i) solvent-dependent self-association of the catalyst via its carbonyl group, (ii) solvent-dependent π-π-donor acceptor interactions of the aryl group in the side chain substituent R_1 with the iminium part of the nitrone, and (iii) solvent-dependent change of the conformer ratio **11**/**12** Inspection of molecular models of the oxazaborolidine-nitrone complex suggests that the flexible benzylic group (R_2= $PhCH_2$) can shield one of the two faces of the nitrone by rotation around the N-CH_2 bond The complexicity of the system and the differences in enantioselectivities observed for a given catalyst between nitrone **1** and **7** do not allow us to speculate in more detail about the transition state at this moment

re



si



11 **12**

In order to gain further insight in the chiral recognition mechanism the effect of the solvent in asymmetric 1,3-dipolar cycloadditions of other nitrones needs to be investigated As to this, rigid nitrones with a fixed geometry are particularly interesting because they display a reduced degree of freedom Of interest are also C-alkyl nitrones, which can give more information with regard to the occurrence of attractive π-π interactions in the transition state controlling the enantioselectivity

4.4 Conclusions

From the results presented in this chapter the following conclusions can be drawn

1) The asymmetric 1,3-dipolar cycloaddition of nitrones **1** and **7** with 1,1-dialkoxypropenes **2** and **8** is strongly catalyzed by 10-20 mol% chiral oxazaborolidines **3**, derived from N-tosyl-*L*-α-amino acids and borane-tetrahydrofuran or borane-dimethylsulfide, at -78 °C The reactions proceed with complete regio- and stereoselectivity to give the corresponding *cis*-3-phenyl-4-

methyl-5,5-dialkoxyisoxazolidines in high yields

2) The enantioselectivity can be optimized to reasonable levels (*ca* 90 10 ratio of enantiomers) by varying the structure of the ligand and the solvent
3) Opposite enantiofacial selectivities are obtained in cycloaddition reactions with nitrone **1** catalyzed by *L*-tyrosine(O-benzylether) derived oxazaborolidine **3a** (up to 62% ee of (-)-**4**) or *L*-isoleucine (up to 73% ee of (+)-**4**)
4) The addition of *ligand-like* co-solvents, e g dibenzylether and diphenylether, to the **3a**-catalyzed reaction of nitrone **1** leads to a dramatic reversal of the enantioselectivity (up to 79% ee of (+)-**4**)
5) The presence of aromatic solvents, e g toluene, in the reaction of nitrone **7** catalyzed by oxazaborolidines having an aromatic ring in their side-chain substituent leads to a reversal of enantioselectivity (up to 74% ee of (*2S,3S*)-**10**)
6) These results open the possibility to prepare both enantiomers of nitrone cycloadducts in a stereoselective way, starting from a single chiral source by addition of appropiate ligand-mimicking donor-solvents[13]

4.5 Experimental Section

Dichloromethane was dried and distilled on CaH_2 and all other solvents were stored over 4Å molecular sieves Diphenyl ether was melted before use All reactions were carried out under dry nitrogen or argon atmosphere ^{1}H-NMR spectra and ^{13}C-NMR were recorded on a Varian EM 390 (90 MHz, CW), a Bruker AM-100 (100 MHz, FT) or a Bruker AM-400 (400 MHz, FT) spectrometer with TMS as the internal standard Gas chromatography was performed on a Hewlett-Packard 5710A GC-instrument equipped with a capillary HP cross-linked methyl silicone (25 m x 0 31 mm) column type PAS 017 Melting points were measured with a Reichert Thermopan microscope and are uncorrected Optical rotation was measured with a Perkin Elmer 241 polarimeter Enantioselectivities were determined by HPLC analysis using a LKB 2225 HPLC apparatus and chiral Daicel CHIRALCEL OD and CHIRALPAK AD columns with hexane/2-propanol mixtures as eluent Nitrones **1** and **7**[1h,14], ketene acetals **2** and **8**[21] and N-tosyl α-amino acids[8] were prepared according to literature procedures

Chiral oxazaborolidine catalyzed 1,3-dipolar cycloaddition of nitrones with ketene acetals (General procedure)

The chiral oxazaborolidines (0 2 mmol) were prepared *in situ* from N-tosyl-*L* α-amino acids[8] at room temperature under an inert nitrogen atmosphere by addition of equimolar amounts of BH_3 THF (1M solution in THF) or BH_3 SMe_2 (1M solution in CH_2Cl_2 or 1M solution in toluene) in dry solvent (total volume 4 ml)[3a] Nitrone (1 0 mmol) was added at room temperature, the mixture cooled to 78 °C and the ketene acetal (1 5-3 equiv) was added After 5-24 hrs the nitrone was completely converted and the reaction mixture was quenched with saturated aqueous bicarbonate, extracted with

dichloromethane and diethyl ether, dried with Na_2SO_4 and concentrated under vacuum The crude 5,5-dialkoxyisoxazolidine was isolated in 80-99% yield Samples (*ca* 10 mg) for HPLC analysis were further purified by flash chromatography on silica gel or alumina using ether *n*-hexane (1 1-4, v/v, containing 1% Et_3N) as eluent followed by concentration under vacuum

2,3-Diphenyl-4-methyl-5,5-diethoxy-isoxazolidine 4[3c]

M p 93 °C, 400 MHz ^{1}H NMR δ(ppm) 0 78 3H, d, J = 7 2 Hz, 4-CH_3, 0 90 3H, t, J = 7 1 Hz, CH_3, 1 29 3H, t, J = 7 1 Hz, CH_3, 2 84 1H, quintet, J = 7 1 Hz and J = 6 9 Hz, H-4, 3 54-3 74 4H, m, 2x O-CH_2, 4 99 1H, d, J = 6 9 Hz, H-3, 6 87 3H, m, ArH, 7 16 2H, m, ArH, 7 31 3H, m, ArH, 7 41 2H, m, ArH ^{13}C NMR δ(ppm) 11 1 (4-CH_3), 14 6 (CH_3), 15 0 (CH_3), 46 0 (C-4), 57 3 (CH_2), 59 5 (CH_2), 72 3 (C-3), 114 7, 120 9 (C 5), 121 0, 127 3, 127 4, 128 3, 128 5, 138 5 (C_{ipso}), 151 5 (C_{ipso}) HRMS (rel int) m/e 328 (M^{+1}, 7), 327 (M^+, 34), 282 (-OEt, 37), 226 (12), 219 (95), 208 (10), 180 (51), 145 (56), 135 (38), 130 (100) Peak Match M_{calc} = 327 1834, M_{found} = 327 18337 ±0 00096 $C_{20}H_{25}NO_3$ Calc C 73 37, H 7 70, N 4 28 Found C 73 36, H 7 70, N 4 34 A sample of (-)-**4** with 62% enantiomeric purity gave an optical rotation of $[\alpha]_D^{25}$ = 57° (*c* = 0 5 in $CHCl_3$) The enantioselectivity of the reaction was determined by HPLC using a CHIRALPAK AD column, UV detection at 254 nm, flow rate 0 75 ml/min , eluent *n*-hexane/2-PrOH = 98/2 (v/v), 9 53 min (minor isomer) and 10 62 min (major isomer) or at flow rate 1 0 ml/min , eluent *n*-hexane/2-PrOH = 99/1 (v/v), 10 10 min (minor isomer) and 11 47 (major isomer) The absolute configurations of (+)- and (-)-**4** are not known

5,5-Dimethoxy-4-methyl-3-phenyl-N-benzyl isoxazolidine 9

Oil, 400 MHz ^{1}H NMR δ (ppm) 0 78 3H, $J_{4CH3,H3}$=7 29 Hz, 4-CH_3, 2 73 1H, dq, $J_{H4\ 4CH3}$=7 18 Hz, $J_{H4\ H3}$=6 90 Hz, H 4, 3 28 3H, s, 5-OCH_3, 3 36 3H, s, 5-OCH_3, 3 88 1H, d, J_{gem}=14 4 Hz, H-6a, 4 02 1H, d, J_{gem}=14 4 Hz, H-6b, 4 45 1H, d, $J_{H3\ H4}$=6 9 Hz, H-3, 7 31 10H, m, H-arom ^{13}C NMR δ(ppm) 10 8 (4-CH_3), 46 0 (C-4), 49 5 (5-OCH_3'), 50 5 (5-OCH_3), 61 9 (Ph$\underline{C}H_2$), 73 3 (C-3), 121 0 (C-5), 127 0 (C-Ar), 127 2 (C-Ar), 127 5 (C-Ar), 127 9 (C-Ar), 128 1 (C-Ar), 128 2 (C-Ar), 128 3 (C Ar), 128 6 (C-Ar), 129 0 (C-Ar), 129 3 (C-Ar), 137 0 (C_{ipso}), 137 8 (C_{ipso}) HRMS (rel int) m/e 314 (M^++1, 2), 313 (M^+, 10), 282 (-OCH_3, 2), 267 (-CH_3, 2), 226 (2), 213 (6), 212 (40), 194 (5), 191 (16), 149 (16), 121 (25), 102 (51), 91 (100) Peak Match M_{calc} = 313 1678, M_{found} = 313 1672 ± 0 0009 Isoxazolidine **9** is not stable on silica gel and its purification by chromatography on silica gel gave an oil in low yield Hydrogenolysis of the crude isoxazolidine **9** gave the corresponding β-amino ester **10** in high yields (*vide infra*)

Methyl (2R,3R)-3-amino-2-methyl-3-phenylpropionate 10[17]

To a solution of the crude isoxazolidine **9** (313 mg, 1 mmol) in methanol-water-acetic acid (20 2 1, v/v/v, 10 ml) was added $Pd(OH)_2$ on carbon (Pearlman s catalyst, 250 mg) and the resulting black suspension was stirred under a hydrogen balloon for 5 hrs The reaction mixture was filtered through a plug of Celite, the latter was washed with methanol and the filtrate was concentrated to give a white residue This residue was dissolved in sat aq $NaHCO_3$ and the solution was subsequently extracted

with dichloromethane The combined organic extracts were dried ($MgSO_4$), filtered and evaporated to afford the free β-amino ester (2R,3R)-**10** (175 mg, 90% yield) Samples (*ca* 10 mg) for HPLC analysis were further purificied by flash chromatography on silica gel using methanol ether (30 1, v/v) as eluent followed by concentration under vacuum The absolute configuration *2R,3R* of **10** was established from the fact that this compound displayed a negative optical rotation, the enantiomer (*2S,3S*)-**10** was reported to give positive rotation $[\alpha]_D^{25}$ = +15 8 (*c* = 1 00, $CHCl_3$)[17] The enantiomeric excess was determined by HPLC using a chiral HPLC column, type Daicel CHIRALCEL OD, UV detection at 226 nm, eluent *n*-hexane/2-PrOH = 99/1 (v/v), flow rate 1 0 ml/min , (*2R,3R*)-**10** 22 2 min , (*2S,3S*)-**10** 36 0 min The enantioselectivity of the reaction could also be determined by NMR on the diastereomeric Mosher derivatives of **10** The β-amino ester (*2S,3S*)-**10** (HPLC 57% ee) was dissolved in dichloromethane and (*R*)-Mosher acid chloride was added[18] After stirring at room temperature for 2 hrs the crude mixture was separated by flash chromatography on silica gel to afford the pure Mosher amide as a mixture of two diastereomers Oil, 400 MHz ^{1}H NMR δ (ppm) 1 11 0 64H, d, J = 7 1 Hz, 2-CH_3 (2R,3R), 1 17 2 36H, d, J = 7 1 Hz, 2-CH_3 (2S,3S), 3 02 1H, m, H-2, 3 38 0 64H, s, OMe, 3 47 2 36H, s, OMe (2S,3S), 3 56 0 64H, s, OMe, 3 60 2 36H, s, OMe (2S,3S), 5 32 1H, m, H-3, 7 13 1H, m, NH, 7 23-7 43 10H, m, ArH ^{13}C NMR δ (ppm) 12 8 (2-Me, (2R,3R)), 13 1 (2-Me, (2S,3S)), 44 4 (C 2, (2R,3R), 44 5 (C-2, (2S,3S)), 51 9 (OMe), 55 0 and 55 1 (OMe), 77 2, 122 3, 125 1, 126 7, 126 9, 127 5, 127 6, 127 8, 128 4, 128 5, 129 4, 129 8, 132 4, 138 6 (Ar-C), 165 5 (C=O), 173 9 (C=O) ^{19}F NMR δ (ppm) 11 00 s, CF_3 and 11 04 s, CF_3 (2S,3S) The resolution was not good enough to give a reliable integration HRMS (rel int) m/e 410 (M^{+1}, 0 3), 378 (-OMe, 2), 322 (10), 220 (20), 189 (32), 177 (55), 145 (3), 132 (3), 121 (100) Peak Match $C_{21}H_{22}NO_4F_3$ M_{calc} = 409 1500, M_{found} = 409 1501 ± 0 001

4.6 References and notes

† Partially presented at IKCOC-6, november 7-11, 1994, Kyoto, Japan, abstracts OP-33 and PP-092 and taken from Seerden, J -P G , Kuypers, M M M , Scheeren, J W *Tetrahedron Asymmetry* **1995**, *6*, 1441-1450

1 Tufariello, J J in *1,3-Dipolar Cycloadditions Chemistry*, Padwa, A , Ed , Wiley, New York, **1984**, vol 2, pp 83-168, Mulzer, J *Nachr Chem Tech Lab* **1984**, *32*, 882-887, Balasubramanian, N *Org Prep Proc Int* **1985**, 25, Black, D S , Crozier, R F , Davis, V C *Synthesis* **1975**, 205-221, Confalone, P N , Huie, E M *Org React* **1988**, *36*, 1-173, Annunziata, R , Cinquini, M , Cozzi, F , Raimondi, L *Gazz Chim Ital* **1989**, *119*, 253-269, Torssell, K B G , *Nitrile Oxides, Nitrones and Nitronates in Organic Synthesis*, VCH New York, 1992, Dopp, D , Dopp, H in "Houben-Weyl, Methoden der Organischen Chemie , vol E14b, Klamann, D , Hagemann, H , Eds , Georg Thieme Verlag Stuttgart, **1990**

2 See for example Murahashi, S -I , Imada, Y , Kohno, M , Kawakami, T *Synlett* **1993** 395-

396 (ref 2 and 3 cited therein), b) Mukai, C , Kim, I J , Cho, W J , Kido, M , Hanaoka, M *J Chem Soc Perkin Trans 1* **1993**, 2495-2503, c) Murahashi, S -I , Sun, J , Tsuda, T *Tetrahedron Lett* **1993**, *34*, 2645-2648, d) Goti, A , Cicchi, S , Brandi, A , Pietrusiewitz, K M *Tetrahedron Asymmetry* **1991**, *2*, 1371-1378, e) Takahashi, T , Fujii, A , Sugita, J , Hagi, T , Kitano, K , Arai, Y , Koizumi, T , Shiro, M *Tetrahedron Asymmetry* **1991**, *2*, 1379-1390, f) Brandi, A , Cicchi, S , Goti, A , Koprowski, M , Pietrusiewicz, K M *J Org Chem* **1994**, *59*, 1315-1318, g) Wovkulich, P M , Baggiolini, E G , Hennessy, B M , Uskokovic, M R *Heterocycles* **1993**, *35*, 791-797, h) Tamura, O , Yamaguchi, T , Noe, K , Sakamoto, M *Tetrahedron Lett* **1993**, *34*, 4009-4010, i) Tamura, O , Yamaguchi, T , Okabe, T , Sakamoto, M *Synlett* **1994**, 620-622, j) Konosu, T , Oida, S *Chem Pharm Bull* **1993**, *41*, 1012 1018, k) Keller, E , de Lange, B , Rispens, M T , Feringa, B L *Tetrahedron* **1993**, *49*, 8899-8910, Rispens, M T , Keller, E , de Lange, B , Zijlstra, R W J , Feringa, B L *Tetrahedron Asymmetry* **1994**, *5*, 607-624, l) Gravestock, M B , Knight, D W , Lovell, J S , Thornton, S R *J Chem Soc Perkin Trans 1* **1994**, 1661-1663, m) Saito, S , Ishikawa, T , Moriwake, T *J Org Chem* **1994**, *59*, 4375-4377, n) Naito, T , Ikai, M , Shirakawa, M , Fujimoto, K , Ninomiya, I , Kiguchi, T *J Chem Soc Perkin Trans 1* **1994**, 773-775, o) Aurich, H G , Quintero, J -L R *Tetrahedron* **1994**, *50*, 3929-3942, p) Oppolzer, W , Deerberg, J , Tamura, O *Helv Chim Acta* **1994**, *77*, 554-560

3 a) Seerden, J -P G , Scholte op Reimer, A W A , Scheeren, J W *Tetrahedron Lett* **1994**, *35*, 4419-4422, b) the absolute configuration of cycloadduct **4** is arbitrarily chosen For other non-catalytic examples of 1,3-dipolar cycloaddition of nitrones with ketene O,O dialkyl acetals see c) Scarpati, R , Sica, D , Santacroce, C *Gazz Chim Ital* **1966**, *96*, 375-386, and d) Huisgen, R , Grashey, R , Seidl, H , Hauck, H *Chem Ber* **1968**, *101*, 2559-2563 For reaction of chiral nitrones with cyclic ketene acetals see e) Keirs, D , Moffat, D , Overton, K , Tomanek, R *J Chem Soc Perkin Trans 1* **1991**, 1041-1051, For reactions of achiral nitrones with cyclic ketene acetals under microwave irradiation and solvent-free conditions see f) Díaz-Ortiz, A Díez-Barra, E , de la Hoz, A , Prieto, P , Moreno, A *J Chem Soc Perkin Trans 1* **1994**, 3595-3598

4 The alternative concerted reaction mechanism via an *endo*-approach of the ketene acetal would be accompanied by unfavorable steric interactions between the 2-methyl substituent of the ketene acetal and the C-phenyl group of the nitrone

5 Seerden, J -P G , Scheeren, J W *Tetrahedron Lett* **1993**, *34*, 2669-2672

6 For examples of attractive donor-acceptor interactions in catalytic asymmetric Diels-Alder reactions see Corey, E J , Roper, T D , Ishihara, K , Sarakinos, G *Tetrahedron Lett* **1993**,*34*, 8399, Ishihara, K , Yamamoto, H *J Am Chem Soc* **1994**, *116*, 1561, Hawkins, J M , Loren, S , Nambu, M *J Am Chem Soc* **1994**, *116*, 1657 Review Sawamura, M , Ito, Y *Chem Rev* **1992**, *92*, 857-871

7 a) Other important variables in the system are the mode of preparation, age, and enantiomeric purity of the catalyst, e g see Sartor, D , Saffrich, J , Helmchen, G , Richards, C J , Lambert, H *Tetrahedron Asymmetry* **1991**, *2*, 639-642, b) for a discussion of association

processes of oxazaborolidines, see Brown, J B , Lloyd-Jones, G C , Layzell, T P *Tetrahedron Asymmetry* **1993**, *4*, 2151-2154, Nevalainen, V *Tetrahedron Asymmetry* **1991**, *2*, 827-842

8 a) Houben-Weyl, *'Methoden der Organischen Chemie'*, Band 15/1, *Synthese von Peptiden* I, 4eAuflage, Georg Thieme Verlag, Stuttgart, **1974**, pp 223-233, b) Berry, M B , Craig, D *Synlett*, **1992**, 41-44

9 a) Carlson, R , Lundstedt, T , Albano, C *Acta Chem Scand B*, **1985**, *39*, 79 91, b) Reichardt, C *Angew Chem* **1979**, *91*, 119-131

10 Reichardt, C , 'Solvents and Solvent Effects in Organic Chemistry , 2nd ed , **1990**, VCH, Weinheim

11 For examples of solvent-dependent enantioselectivity in chiral Lewis acid catalyzed asymmetric Diels-Alder and aldol reactions see Corey, E J , Loh, T -P *Tetrahedron Lett* **1993**, *34*, 3979-3982, Corey, E J , Guzman-Perez, A , Loh, T -P *J Am Chem Soc* **1994**, *116*, 3611-3612, Ishihara, K , Gao, Q , Yamamoto, H *J Org Chem* **1993**, *58*, 6917 6919, Kobayashi, S , Fujishita, Y , Mukaiyama, T *Chem Lett* **1990**, 1455-1458, Kobayashi, S , Uchiro, H , Shiina, I , Mukaiyama, T *Tetrahedron* **1993**, *49*, 1761-1772 In other reactions Hiroi, K , Arinaga, Y , Ogino, T *Chem Lett* **1992**, 2329, Froelich, O , Bonin, M , Quirion, J -C , Husson, H -P *Tetrahedron Asymmetry* **1993**, *4*, 2335-2338, Soai, K , Suzuki, T , Shono, T *J Chem Soc , Chem Commun* **1994**, 317-318, Hansen, T V , Waagen, V , Partali, V , Anthonsen, H W , Anthonsen, T *Tetrahedron Asymmetry* **1995**, *6*, 499-504, Aune, M , Gogoll, A , Matsson, O *J Org Chem* **1995**, *60*, 1356 1364, see also ref 10, pp 244-260

12 The usual oxazaborolidine catalyst preparation introduces *ca* 12 equiv THF (from 1M BH_3 THF in THF) in the reaction mixture Only 2% ee was obtained when the **3a**-catalyzed reaction was performed in THF

13 a) For examples of solvent-dependent reverse enantiofacial selectivities see Ando, K , Takemasa, Y , Tomioka, K , Koga, K *Tetrahedron* **1993**, *49*, 1579, b) Kobayashi, S , Ishitani, H *J Am Chem Soc* **1994**, *116*, 4083-4084, Kobayashi, S , Ishitani, H , Hachiya, I , Araki, M *Tetrahedron* **1994**, *50*, 11623-11636, c) the role of nitroethane is more difficult to understand Strong solvation of the nitrone may hinder the usual attack of the ketene acetal Attack on the rear side may be faster than desolvation, d) Fidler, J , Rodger, A *J Am Chem Soc* **1994**, *116*, 7266

14 General procedures for the synthesis of N benzyl nitrones are a) the reaction of carbonyl compounds with hydroxylamines Dondoni, A , Franco, S , Junquera, F , Merchán, F , Merino, P , Tejero, T *Synth Commun* **1994**, *24*, 2537-2550, b) Catalytic oxidation of *N,N*-disubstituted hydroxylamines with NMO/TPAP Goti, A , De Sarlo, F , Romani, M *Tetrahedron Lett* **1994**, *35*, 6571-6574, c) Oxidation of secondary amines Murahashi, S -I , Shiota, T , Imada, Y *Org Synth Vol 70*, **1992**, 265-271

15 Recently much attention has been paid to the stereoselective preparation of β-amino acids, for reviews, see Cole, D C *Tetrahedron* **1994**, *50*, 9517, Juaristi, E , Quintana, D Escalante J

Aldrichimica Acta **1994**, *27*, 3

16 Pearlman, W M *Tetrahedron Lett* **1967**, *17*, 1663

17 a) Davies, S G , Garrido, N M , Ichihara, O , Walters, I A S *J Chem Soc , Chem Commun* **1993**, 1153 1155, b) Davies, S G , Ichihara, O , Walters, I A S *J Chem Soc , Perkin Trans I* **1994**, 1141-1147, c) Preparation of corresponding trans-**10** see Davies, S G , Walters, I A S *J Chem Soc , Perkin Trans I* **1994**, 1129-1139

18 Preparation of the Mosher-amides was carried out according to Dale, J A , Mosher, H S *J Am Chem Soc* **1973**, *95*, 512

19 The use of *o* xylene, *m*-xylene or naphtalene as co solvents did not improve the enantioselectivity

20 a) From NMR studies both on the nitrones and their BF_3-complexes we found that *E* and *Z*-nitrones can isomerize rapidly in the presence of Lewis acids, b) for references on *Z*-geometry of **1** see Koyano, K , Suzuki, H *Tetrahedron Lett* **1968**, 1859, Koyano, K , Suzuki, H *Bull Chem Soc Jpn* **1969**, *42*, 3306, c) for reference on *E*-geometry of **1** see Bravo, P , Bruche, L , Farina, A , Fronza, G , Meille, S V , Merli, A *Tetrahedron Asymmetry* **1993**, *4*, 2131 2134, d) preparation of BF_3-nitrone complexes Zeeh, B *Synthesis*, **1968**, 37, Minkin, V I , Medyantseva, E A , Andreeva, I M , Yureva, V A *Zhur Org Khim* **1974**, *10*, 2597, e)*E/Z* stereochemistry Bjørgo, J , Boyd, D R , Neill, D C , Jennings, W B *J Chem Soc , Chem Commun* **1974**, 478 479, Jennings, W B , Boyd, D R , Waring, L C *J Chem Soc , Perkin II* **1976**, 610-613, Bjørgo, J , Boyd, D R , Neill, D C , Jennings, W B *J Chem Soc , Perkin I* **1977**, 254

21 Scheeren, J W , Aben, R W M , Ooms, H J , Nivard, R J F *J Org Chem* **1977**, *42*, 3128-3132, J W Scheeren, "Keten-O,O-acetale" in Houben-Weyl, '*Methoden der Organischen Chemie*', H Kropf, E Schaumann (Eds), Georg Thieme Verlag, Stuttgart, **1993**, Band E15, 1674-1736

CHAPTER 5

Asymmetric 1,3-Dipolar Cycloaddition Reactions of Nitrones with Vinyl Ethers Catalyzed by Chiral Oxazaborolidines

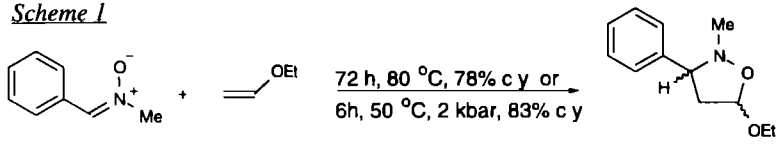
5.1 Introduction

The thermal asymmetric 1,3-dipolar cycloaddition of (chiral) nitrones with (chiral) dipolarophiles has been extensively utilized in the total synthesis of structurally diverse natural products[1,2] Most attention has been paid to the use of electron-deficient dipolarophiles Only few examples with electron-rich dipolarophiles, such as ketene O,O-dialkyl acetals[3,4] or alkyl vinyl ethers[5,6], are known from the literature The 1,3 dipolar cycloadducts of nitrones with these electron-rich dipolarophiles can be considered as being versatile chiral synthetic intermediates for e g γ amino alcohols, β-amino aldehydes, or β-amino esters In Chapters 3 and 4 we reported the first examples of chiral Lewis acid catalyzed 1,3-dipolar cycloaddition of nitrones with ketene acetals The reactivity of nitrones toward ketene O,O-acetals was considerably enhanced by applying chiral oxazaborolidines as Lewis acid catalysts[3f] at -78 °C The chiral Lewis acid is assumed to complex with the nitrone oxygen atom, by which the LUMO energy of the nitrone is lowered to give a $LUMO_{nitrone}$ controlled enantioselective reaction with the electron-rich ketene acetals The cycloadducts were easily converted into the corresponding β-amino esters To establish the generality of this approach[7], the chiral oxazaborolidine catalyzed asymmetric 1,3-dipolar cycloaddition of nitrones with vinyl ethers as a possible route to masked β-amino aldehydes was studied The results of this study are reported in this chapter

Under thermal conditions the 1,3-dipolar cycloaddition of nitrones with mono-substituted alkenes often gives a mixture of *anti*- and *syn*-adducts The 1,3-dipolar cycloaddition reaction of C phenyl N-methyl nitrone **1** with ethyl vinyl ether **2** has been extensively studied under thermal and high pressure conditions by Dicken and DeShong (*Scheme 1*)[5a] Under the former conditions (72 h at 80 °C, without solvent) the isoxazolidine **3** was obtained as an equimolar mixture of *endo* and *exo* isomers in 78% yield (see also Table 1) Application of high pressure (6 h, 2 kbar, 50 °C, no solvent, 35 equiv ethyl vinyl ether) furnished the cycloadduct in 83% chemical yield but again

without any stereoselectivity (50/50 *endo/exo*)

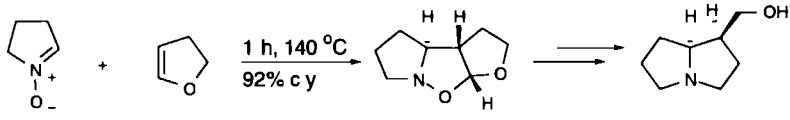
Scheme 1



1 **2** 50/50 endo/exo- **3**

Kakisawa *et al* reported that the rigid and reactive *E*-nitrone pyrroline N-oxide **4** undergoes a stereoselective 1,3-dipolar cycloaddition with the *Z*-enol ether 2,3-dihydrofuran **5** at high temperature to give exclusively the tricyclic *exo*-isoxazolidine **6** in high yield (*Scheme 2*)[5c] The cycloadduct was conveniently transformed after several steps into isoretronecanol **7**[8], a pyrrolizidine alkaloid with interesting biological properties[9]

Scheme 2



4 **5** exo-**6** **7**

The formation of only one of the four possible isomers (two *endo* and two *exo* enantiomers) via asymmetric synthesis is often desired for the preparation of optically pure natural products To achieve this goal chiral nitrones and chiral dipolarophiles have been widely used in contrast to chiral Lewis acids It can be expected that the latter catalysts enhance the reaction rate and in addition to this control the regio-, stereo- and enantioselectivity of the 1,3-dipolar cycloaddition of nitrones with vinyl ethers

5.2 Results and discussion

5.2.1 Catalytic asymmetric reactions of C-phenyl-N-methyl nitrone with ethyl vinyl ether

Analogous to the reaction of nitrones with ketene acetals we found that the reaction of C phenyl N methyl nitrone with ethyl vinyl ether (3 equiv) was strongly catalyzed by 20 mol% of chiral oxazaborolidine **8** (*in situ* derived from the sulfonamide of *L*-serine(O-benzyl ether) and BH_3 THF) in dichloromethane at room temperature and gave complete conversion of the nitrone after 18 hours (*Scheme 3*) After aqueous work-up the crude isoxazolidine product **3** was isolated in 64% yield as a 40/60 mixture of *syn* and *anti* isomers which were separated by column chromatography and analyzed by 400 MHz ^{1}H- and ^{13}C-NMR spectroscopy (Table 1) The reaction was completely regioselective Such a regioselective formation of the 5-dialkoxyisoxazolidine **3** is in agreement with a $LUMO_{nitrone}$ controlled 1,3-dipolar cycloaddition according to the FMO (Frontier Molecular Orbital) theory[7] Unfortunately, in addition to the poor

endo/exo (*syn/anti*) selectivity the enantioselectivity of the reaction was also very poor (< 1% ee)

Because ethyl vinyl ether is less reactive than simple ketene acetals we also studied the effect of high-pressure It is known that irrespective of the nature of the 1,3-dipole, the type of dipolarophile and the solvent, 1,3-dipolar cycloaddition reactions in the liquid phase have an activation volume ($\Delta V^{\ddagger}$) in the range of -18 to -24 $cm^3\ mol^{-1}$, which is approximately 10 $cm^3\ mol^{-1}$ less negative than $\Delta V^{\ddagger}$ for the usual 1,4-cycloaddition (e g Diels-Alder) reaction[10] The dependence of the enantioselectivity on the pressure in a chiral Lewis acid catalyzed reaction has been studied in only one case Tietze *et al* [10c] reported increased enantioselectivity for an intramolecular hetero-Diels-Alder reaction catalyzed by a chiral titanium Lewis acid under high pressure The pressure dependence of the enantioselectivity was assumed to originate from a difference in activation volume of the two possible diastereomeric transition state structures

Scheme 3

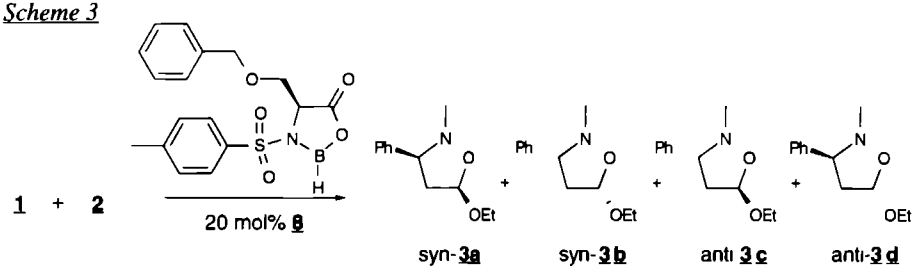


Table 1 Influence of temperature, chiral Lewis acid catalyst and high pressure on 1,3-dipolar cycloaddition of C-phenyl-N-methyl nitrone **1** with ethyl vinyl ether **2**

entry	temp (°C)	pressure (bar)	time (hours)	catalyst (20 mol%)	c y (%)	syn/anti-**3**
1	80	1	72		78[a]	50/50[5a]
2	50	2000	6	-	83[a]	50/50[5a]
3	r t	1000	72	-	0[a]	-[5a]
4	r t	2000	72	-	25[a]	50/50[5a]
5	r t	1	18	**8**	64	40/60
6	r t	2000	18	-	0	-
7	r t	2000	18	**8**	84	42/58

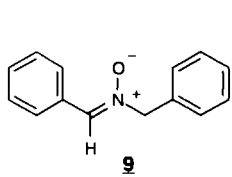
[a] The reaction was carried out without solvent, *ca* 35 equiv of ethyl vinyl ether was added

The results of Table 1 show that under high pressure (2000 bar) the reaction does not proceed at room temperature without a catalyst (entry 6) In the presence of a catalytic amount of chiral Lewis acid **8** the reaction proceeds well at room temperature and at normal pressure (entry 5) The combination of chiral oxazaborolidine **8** and high pressure gave a slight improvement of the yield (entry 7) The chemical yield of this Lewis acid catalyzed reaction in solution with 3 equiv of ethyl vinyl ether is similar to the yield of the reaction under thermal conditions at 80 °C which was

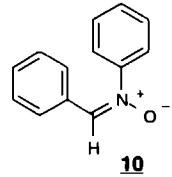
carried out without solvent in the presence of *ca* 35 equiv of ethyl vinyl ether (entry 1) High pressure had no effect on the enantioselectivity which turned out to be again disappointingly low in both cases (< 1% ee)

5.2.2 Catalytic asymmetric 1,3-dipolar cycloadditions of other nitrones with ethyl vinyl ether

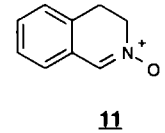
With the above results at hand it was of interest to investigate whether more reactive nitrones could enhance the stereoselectivity and the enantioselectivity of the chiral oxazaborolidine catalyzed 1,3-dipolar cycloaddition reactions with ethyl vinyl ether For this reason (in order of reactivity) C-phenyl N-benzyl nitrone **9**, C,N-diphenyl nitrone **10**, the rigid *E*-nitrone 3,4-dihydroisoquinoline **11** and C-benzoyl-N-phenyl nitrone **12** were explored The effect of high pressure on the outcome of the cycloaddition reactions was also studied



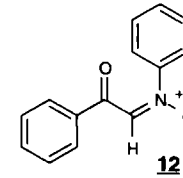
9



10



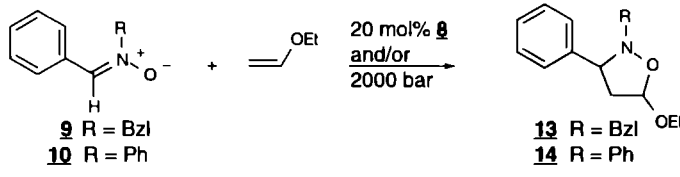
11



12

The 1,3-dipolar cycloaddition of C-phenyl-N-benzyl nitrone **9** with ethyl vinyl ether was nicely catalyzed by 20 mol% chiral oxazaborolidine catalyst **8** at room temperature (*Scheme 4*, Table 2, entry 1) After 21 hours the corresponding N-benzyl-5-ethoxy-isoxazolidine **13** was regioselectively formed in 80% yield, however with poor stereoselectivity (*syn/anti* = 40/60) and no enantioselectivity (< 1% ee) Without a catalyst no reaction occurred at room temperature or under high pressure conditions (2000 bar) (entry 2) The combination of high pressure (2000 bar) and 20 mol% of chiral oxazaborolidine **8** had no effect on the stereo- or enantioselectivity (entry 3)

Scheme 4



9 R = Bzl
10 R = Ph

13 R = Bzl
14 R = Ph

The thermal 1,3-dipolar cycloaddition of C-phenyl-N-phenyl nitrone **10** with excess ethyl vinyl ether was reported by Paul *et al* [11] to give the corresponding N-phenyl-5-ethoxy-isoxazolidine **14** in 75% yield after 14 hours refluxing (Table 2, entry 4) We found that this reaction was catalyzed by 20 mol% chiral oxazaborolidine catalyst **8** at room temperature in dichloromethane solution using only 3 equiv of ethyl vinyl ether (*Scheme 4*) After 21 hours the N-phenyl-5-ethoxy isoxazolidine **14** (m p 83°C, lit [11] m p 83°C) was formed regioselectively in 56% yield as a 37/63 mixture of syn- and anti-isomers (entry 5) The enantioselectivity was very

low (< 1% ee). Without a catalyst under high pressure conditions (2000 bar) the reaction gave a low yield (14%), although complete *syn*-stereoselectivity was observed (entry 6). The combination of 20 mol% chiral oxazaborolidine catalyst **8** and high pressure (entry 7) gave similar results as the reaction of entry 5 with a comparable yield and stereo- and enantioselectivity.

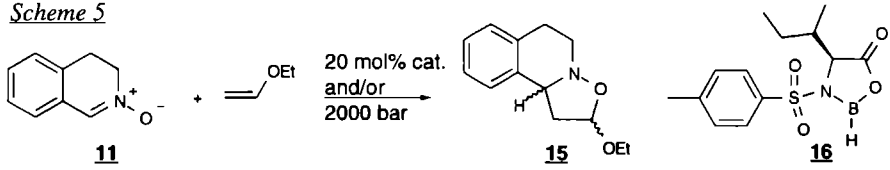
Table 2. Influence of Lewis acid catalyst and high pressure on 1,3-dipolar cycloaddition of nitrone **9** and **10** with ethyl vinyl ether **2** at room temperature

entry	nitrone	pressure (bar)	time (hours)	catalyst (20 mol%)	c y. (%)	product	syn/anti
1	**9**	1	21	**8**	80	**13**	40/60
2		2000	18	-	0		-
3		2000	19	**8**	65		40/60
4	**10**	1	14	-	75[a]	**14**	a
5		1	21	**8**	56		37/63
6		2000	18	-	14		100/0
7		2000	19	**8**	60		38/62

[a] Ref 11, the reaction mixture was refluxed without solvent in excess ethyl vinyl ether, no comments on *syn/anti* stereoselectivity were made.

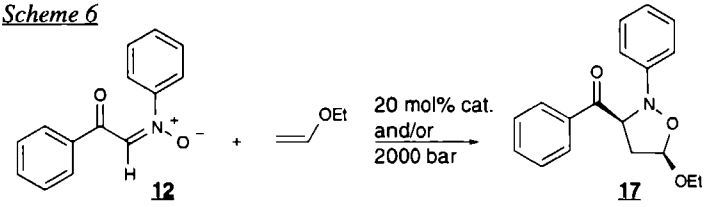
Next, the more reactive nitrones **11** and **12** were studied in the reaction with ethyl vinyl ether under chiral Lewis acid and/or high pressure conditions (*Scheme 5* and *Scheme 6*). Besides chiral oxazaborolidine **8** the *L*-isoleucine-derived oxazaborolidine **16** was also tested.

Scheme 5



11 **15** **16**

Scheme 6



12 **17**

The data of Table 3 show that in the absence of a chiral oxazaborolidine catalyst cyclic nitrone **11**, does not react with ethyl vinyl ether at room temperature in dichloromethane solution (entry 1). Under high pressure conditions and at room temperature the reaction is very sluggish and gives the 5-ethoxy-isoxazolidine cycloadduct **15** in low yields but with good *syn/anti*-stereoselectivity (entries 3 and 5). In the presence of 20 mol% of chiral oxazaborolidine catalyst **16**, cyclic nitrone **11** reacts with ethyl vinyl ether at room temperature to give regioselectively the cycloadduct **15** as a

66/34 mixture of *syn*- and *anti*-isomers in 35% yield (entry 2) The yield is improved when the chiral Lewis acid catalyst is combined with high pressure (entries 4 and 6) However, still poor *syn/anti*-stereoselectivity and no enantioselectivity (< 1% ee) is observed

Table 3 Influence of Lewis acid catalyst and high pressure on 1,3-dipolar cycloaddition of nitrone **11** and **12** with ethyl vinyl ether **2** at room temperature

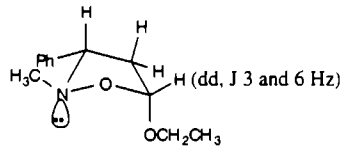
entry	nitrone	pressure (bar)	time (hours)	catalyst (20 mol%)	c y (%)	product	syn/anti
1	**11**	1	18	-	0	**15**	-
2		1	18	**16**	35		66/34
3		1000	20	-	9		93/7
4		1000	20	**8**	41		69/31
5		2000	18	-	14		90/10
6		2000	16	**8**	65		67/33
7	**12**	1	20	-	27[a]	**17**[13]	100/0
8		1	69	**16**	0		-
9		2000	18	-	0		-
10		2000	16	**8**	0		-

[a] The reaction was done following literature procedure ref 13

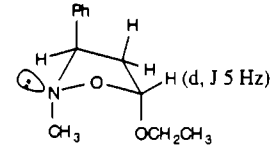
Surprisingly, C-benzoyl-N-phenylnitrone **12**, which is known from the literature to react with unactivated olefines already at ambient temperature[12], gave no reaction at all with ethyl vinyl ether when applying high pressure conditions and/or adding a chiral oxazaborolidine catalyst (entries 8,9 and 10) At room temperature, without a catalyst, the *syn*-3-benzoyl-5 ethoxy-isoxazolidine **17** was formed regio- and stereoselectively in low yield (entry 7) In the original literature[13] the wrong structure was assigned to the cycloadduct[11], i e the 3-benzoyl-4-ethoxy-isoxazolidine isomer was incorrectly denoted as the cycloadduct The double doublet resonance signal observed at 5 43 ppm[13] must obviously correspond to the C-5 acetal proton in the 5 ethoxy cycloadduct The low reactivity under high pressure conditions may be ascribed to selective precipitation or dimerization of the nitrone[5a]

5.2.3 Relative stereochemistry of 5-ethoxy-isoxazolidines

The relative stereochemistry of the isolated syn- and anti-5-ethoxy-isoxazolidines **13**, **14**, **15** and **17** was assigned by analysis of NMR coupling constants and correlation with the known ^{1}H-NMR data of syn- and anti-2-methyl-3-phenyl-5-ethoxy isoxazolidine **3**[5a] Dicken and Deshong have determined both the configuration and the conformation of *syn*- and *anti*-**3** by application of nuclear Overhauser effect difference spectroscopy (NOEDS) in combination with analysis of proton coupling constants[5a]



syn-**3**



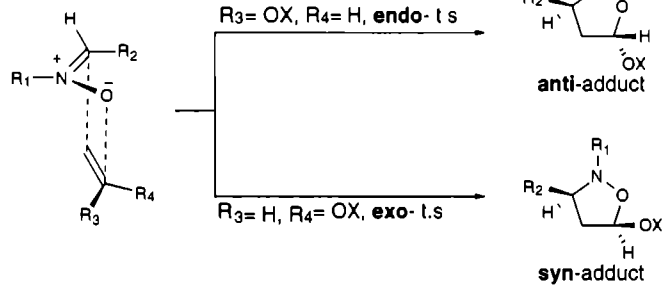
anti-**3**

The NMR signal multiplicities of the acetal protons of *syn*-**3** and *anti*-**3** were remarkably different The *syn*-isomer displayed a doublet of doublets at δ 5 15 ppm with coupling constants of 3 and 6 Hz, whereas the *anti*-isomer showed only a doublet (J = 5 Hz) at δ 5 16 ppm A second feature gave information concerning the preferred conformation of *anti*-**3** in solution. Irradiation of the signal corresponding to the protons of the N-methyl group resulted in enhancement of the O-ethyl protons This indicates that the N-methyl group and the O-ethyl group of *anti*-**3** occupy psuedoaxial positions on the five-membered ring. This orientation takes advantage of the stabilization by an anomeric effect between a lone pair on the ring and the pseudoaxial O-ethyl substituent at C-5 Similar patterns have been consistently obtained for the stereoisomers of isoxazolidines **13**, **14**, **15** and **17**, justifying the assignment of relative stereochemistry In addition, these data show that the preferred conformations of these isoxazolidines in solution are similar to those determined for *syn*- and *anti*-**3**[5a].

5.2.4 Stereochemical considerations of nitrone cycloaddition reactions with ethyl vinyl ether

Knowing the configurations of cycloadducts **3**, **13**, **14**, **15** and **17** some conclusions can be drawn concerning the transition-state geometries of the nitrone cycloadditions with ethyl vinyl ether. Conceptually, cycloaddition of a *Z*-nitrone, e g **1**, **9**, **10** and **12**, with a vinyl ether via a concerted *endo* transition state will result in the formation of the *anti*-isoxazolidine and cycloaddition through the *exo* transition state will give the *syn* isomer, as shown in Scheme 7

Scheme 7



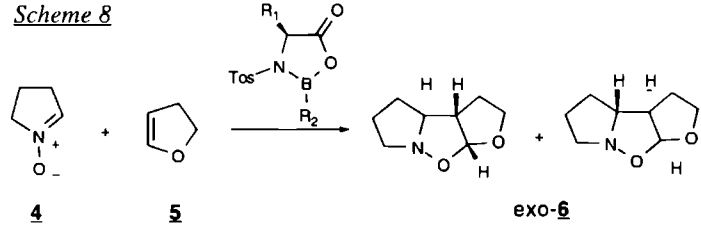
Similarly, *endo*- or *exo*-cycloaddition of an *E*-nitrone, e g **11**, will result in the formation of the *syn*- or *anti*-isoxazolidine, respectively. In the presence of a chiral oxazaborolidine catalyst the cycloadditions of nitrones with ethyl vinyl ether gave mixtures of *syn*- and *anti*-isomers This means that there is no discrimination between the *endo* and *exo* transition states during the

cycloaddition reaction, or the cycloadducts are formed from nitrones which react in their *E*- as well as their *Z*-configuration This result is not surprising, since there is neither secondary orbital overlap to favor the endo transition state nor obvious steric congestion which may develop in either transition state In the absence of a Lewis acid catalyst the application of high pressure can lead to highly preferential formation of the *syn*-isomers, however the yields are low The combination of high pressure and a chiral oxazaborolidine catalyst leads to the same stereoisomeric distribution as is obtained in the presence of a catalyst at normal pressure These results may be rationalized via a the formation of a dipolar intermediate, as has been proposed for the reaction of nitrones with ketene acetals (Chapter 3) However, the results do not allow to draw definite conclusions about the type of transition state of the chiral oxazaborolidine catalyzed 1,3-dipolar cycloaddition of nitrones with ethyl vinyl ether The use of β-substituted *E*- or *Z*-enol ethers may give additional information on the stereochemical course of the reaction with acyclic nitrones[14]

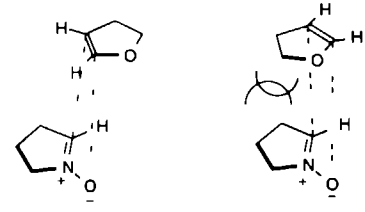
5.2.5 Catalytic asymmetric 1,3-dipolar cycloaddition reactions of pyrroline N-oxide with 2,3-dihydrofuran

The lack of stereo- and enantiocontrol in 1,3-dipolar cycloaddition reactions of nitrones with ethyl vinyl ether observed under thermal, (chiral) Lewis acid and high pressure conditions prompted us to study the effect of chiral oxazaborolidines and high pressure conditions on the *exo*-selective 1,3-dipolar cycloaddition of the rigid *E*-nitrone pyrroline N-oxide **4** with the rigid *Z*-enol ether 2,3-dihydrofuran **5** (*Scheme 8*, Table 4) The reaction appeared to be completely *exo*-stereoselective which can be explained by assuming that pyrroline N-oxide **4** reacts with 2,3-dihydrofuran **5** through *exo*-oriented transition state **18** rather than through *endo* transition state **19**, which is difavored because of steric congestion[5c]

Scheme 8



4 **5** exo-**6**



18 *exo* **19** *endo*

The thermal reaction also proceeded with complete regiostereoselectivity to give 1-aza-2,4-dioxatricyclo[6 3 0 0]undecane *exo*-**6** in 93% yield (Table 4, entry 1), in agreement with literature reports[5c] (92 % yield in 1 hour) In the presence of 20 mol% of oxazaborolidine **8** the reaction did not proceed under standard conditions in dichloromethane as solvent and at room temperature (entry 2)

Table 4 Influence of temperature, Lewis acid and high pressure on the asymmetric 1,3-dipolar cycloaddition of pyrroline N-oxide **4** to 2,3-dihydrofuran **5**[a] (*Scheme 8*)

entry	temp (°C)	pressure (bar)	time (hours)	catalyst R_1	catalyst R_2	yield (%)[b]	e e **6** (%)[c]
1[d]	140	1	7	-	-	93	-
2[e]	r t	1	24	$BnOCH_2$	H	0	-
3[f]	-78	1	6	$BnOCH_2$	H	0	-
4[f]	4	1	18	$BnOCH_2$	H	29	7
5[f]	r t	1	23	$BnOCH_2$	H	65	1
6[f]	"	2000	22		-	65	
7[f]	"	2000	22	$BnOCH_2$	H	69	4
8[f]	"	2000	20	*i*-Bu	H	41	10
9[f]	"	2000	20	*i*-Bu	*n* Bu	70	17
10[f]	"	2000	20	Ph	H	61	30
11[f]	"	2000	20	Ph	*n*-Bu	100	11

[a] 2 3 Dihydrofuran **5** was used as solvent and 20 mol% of oxazaborolidine as catalyst [b] Determined by GLC analysis [c] Determined by HPLC analysis using a Chiralpak AD column UV detection at 210 nm eluent 98/2 (v/v) hexane/2-propanol, 0 75 ml/min , 28 9 min (major isomer) and 30 3 min, [d] Ref 5c, benzene was used as solvent heating in sealed tube [e] CH_2Cl_2 as solvent [f] 2 3-Dihydrofuran as solvent

However, when 2,3-dihydrofuran **5** was used as a dipolarophile and at the same time as the solvent the reaction was catalyzed by chiral oxazaborolidine **8** (R_1 = $BnOCH_2$, R_2 = H) at room temperature to give 65% yield of the cycloadduct **6** with low enantioselectivity (entry 5) At lower temperatures the yield decreased dramatically (entries 3 and 4) Without a Lewis acid catalyst this reaction could be performed under high pressure conditions (2000 bar) and at room temperature in neat 2,3-dihydrofuran to give exclusively *exo*-cycloadduct **6** (65% yield, entry 6) At 2 kbar a catalytic asymmetric 1,3-dipolar cycloaddition reaction could be achieved with chiral oxazaborolidines **8** (R_1 = $BnOCH_2$, R_2 = H, entry 7) and **16** (R_1 = *i*-Bu, R_2 = H, *n*-Bu, entries 8 and 9) It should be noted that the competing non-catalyzed reaction (entry 6) will lower the enantioselectivity under high pressure Remarkably, alkyl-substituted oxazaborolidines (e g R_2 = *n*-Bu), derived from alkylboronic acids, gave better yields (entries 9 and 11) than the corresponding hydrogen-substituted oxazaborolidines (R = H) although it is expected that their Lewis acidity is lower Enantioselectivities up to 30% ee were obtained with a chiral oxazaborolidine catalyst derived from N-tosyl phenylglycine and borane-THF (entry 10)

In order to improve the enantioselectivity of the reaction and to gain insight in the

mechanism of chiral induction, the structure of the oxazaborolidine was further varied The effects of the position of a phenyl group in the side chain substituent R_1, alkyl- or arylsubstitution of the boron atom and the arylsulfonyl part of the oxazaborolidines were investigated at ambient pressure and temperature(Table 5) The results in Table 5 show that a slight reversal of enantioselectivity is achieved with the N-tosyl phenylalanine-derived oxazaborolidine in 2,3-dihydrofuran as solvent (entries 3 and 4) This observation suggests that the position of a phenyl group in the side-chain substituent of the chiral oxazaborolidine catalyst may be relevant for determining the enantioselectivity via attractive donor-acceptor interactions with the nitrone moiety[3d] However, an electron donating 4-benzyloxy substituent did not increase the enantioselectivity (entries 5 and 6) Again, alkyl- or aryl-substituted oxazaborolidines gave higher yields but had no effect on the enantioselectivity (entries 2, 4 and 6)

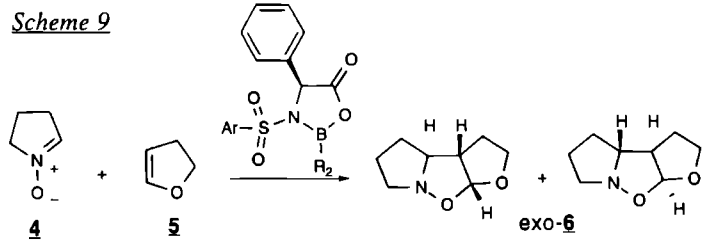
Table 5 Chiral oxazaborolidine catalyzed 1,3-dipolar cycloaddition of nitrone **4** with pyrroline N-oxide **5** at ambient pressure and temperature[a]

entry	catalyst R_1	catalyst R_2	yield (%)	e e **6** (%)[b]
1	Ph	H	56	38
2	Ph	*n*-Bu	74	34
3	$PhCH_2$	H	58	18*[c]
4	$PhCH_2$	Ph	73	16*[c]
5	(4-BnO)Ph-CH_2	H	54	0
6	(4-BnO)Ph-CH_2	Ph	71	18*[c]

[a] 2 3 Dihydrofuran **5** as solvent 20 mol% of oxazaborolidine as catalyst reaction time22 23 hrs [b] Determined by HPLC analysis with Chiralpak AD column UV detection at 210 nm eluent 98/2 (v/v) hexane/2 propanol 0 75 ml/min , [c] opposite enantiomer

The influence of the arylsulfonyl group in the catalyst was studied for the phenylglycine derived oxazaborolidine (R_1 = Ph) which gave the best enantioselectivity (*Scheme 9*, Table 6) Table 6 shows that a 2,4,6 trimethylphenylsulfonyl (mesityl-sulfonyl) substituent (entry 3) as well as a 4-nitrophenylsulfonyl (nosyl) substituent (entry 5) gives reversal of enantioselectivity Alkyl- or aryl-substitution of the boron atom has no effect on the enantioselectivity except for the N nosyl phenylglycine derived oxazaborolidine (entry 6)

Scheme 9



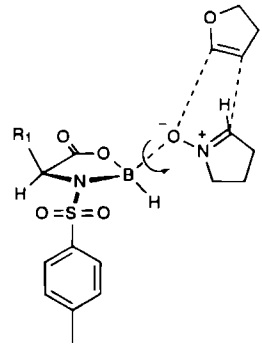
4 **5**

Table 6 Influence of the arylsulfonyl part in the chiral oxazaborolidine catalyst on the 1,3-dipolar cycloaddition of nitrone **4** to pyrroline N-oxide **5**[a] (*Scheme 9*)

entry	catalyst Ar-SO_2	catalyst R_2	yield (%)	e e **6** (%)[b]
1	4-CH_3-Ph	H	56	38
2		*n*-Bu	74	34
3	2,4,6-$(CH_3)_3$-Ph	H	15	11[c]
4		Ph	22	5[c]
5	4-NO_2-Ph	H	86	12[c]
6		Ph	68	34

[a,b,c] See Table 5

It is difficult to draw conclusions with regard to the mechanism that controls the enantioselectivity, as the absolute configuration of the cycloadducts is not known In analogy with the working models that have been proposed for the chiral oxazaborolidine catalyzed Diels-Alder reaction (Chapter 2) and the 1,3-dipolar cycloaddition reaction of nitrones with ketene acetals (Chapter 3 and 4), working model **20** is proposed to rationalize the observed selectivities obtained thus far at room temperature It is assumed that dihydrofuran will attack from the less hindered side of the oxazaborolidine-nitrone complex (i e *Re*-face attack) Effective shielding of one face of the nitrone is strongly dependent on the rotation barrier of the oxazaborolidine-nitrone B-O bond The position of a phenyl ring in R_1 may affect the enantioselectivity, probably via steric effects (R_1= Ph) or by attractive π-π donor-acceptor interactions (R_1= $PhCH_2$)



Re-face attack

"Working Model" **20**

5.3 Conclusions

The results presented in this chapter can be summarized as follows

1) Chiral oxazaborolidines can applied as chiral Lewis acid catalysts in the asymmetric 1,3-dipolar cycloaddition of various nitrones with vinyl ethers under mild conditions The cycloaddition reaction rate is enhanced by high pressure (2000 bar)

2) The reactions of acyclic and cyclic nitrones with ethyl vinyl ether proceed with complete regioselectivity, but with poor stereoselectivity to give mixtures of *syn*- and *anti*-5-ethoxy-isoxazolidines In all cases the enantioselectivity is very low
3) The chiral oxazaborolidine catalyzed *exo*-selective cycloaddition of pyrrolidine N-oxide with excess 2,3-dihydrofuran affords a cycloadduct with moderate enantioselectivity This reaction opens the possibility to construct versatile chiral intermediates for pyrrolizidine alkaloids
4) In order to understand the factors that control the reaction and to obtain higher enantioselectivity further optimization of the reaction parameters and design of the chiral Lewis acid catalysts together with a study of the substituent effects in the vinyl ethers is needed

5.4 Experimental Section

Dichloromethane was dried and distilled from CaH_2 All solvents were stored over 4Å molecular sieves All reactions were carried out under dry nitrogen or argon atmosphere ^{1}H-NMR spectra and ^{13}C-NMR were recorded on a Varian EM 390 (90 MHz, CW), a Bruker AM-100 (100 MHz, FT) or a Bruker AM-400 (400 MHz, FT) spectrometer with TMS as internal standard Gas chromatography was performed on a Hewlett-Packard 5710A GC-instrument equipped with a capillary HP cross-linked methyl silicone (25 m x 0 31 mm) column type PAS 017 Melting points were measured with a Reichert Thermopan microscope and are uncorrected Optical rotation was measured with a Perkin Elmer 241 polarimeter The high pressure apparatus operating at 1-15 kbar has been described before[15] Enantioselectivities were determined by HPLC analysis on a LKB 2225 HPLC apparatus using Daicel CHIRALCEL OD and CHIRALPAK AD columns with hexane/2-propanol mixtures as eluents Racemic products obtained from ZnI_2 catalyzed reactions were used as reference materials for determination of the enantiomeric excess by HPLC Nitrones **1** and **10** were prepared by condensation of benzaldehyde with commercially available N-methyl-hydroxylamine and N-phenyl hydroxylamine[1h], respectively Nitrones **4**, **9**[16] and **11** were prepared by oxidation of the corresponding secondary amines with Na_2WO_6/H_2O_2[17] C benzoyl N-phenyl nitrone **12** was prepared by silver oxide oxidation of the adduct of the silyl enol ether of acetophenone and nitrosobenzene[18] N-Arylsulphonyl *L* α-amino acids[19] and trimethyl(1-phenylvinyloxy)silane **30**[20] were prepared according to literature procedures

A Chiral oxazaborolidine catalyzed 1,3-dipolar cycloaddition of nitrones with ethyl vinyl ether (General procedure)

The chiral oxazaborolidines (0 2 mmol) were prepared *in situ* at room temperature under an inert nitrogen atmosphere from N-tosyl-*L*-α-amino acids[3] by addition of equimolar amounts of BH_3 THF (1M solution in THF, reaction time 10 min) or phenyl- or *n*-butylboronic acid (in the presence of 4Å powdered molecular sieves, reaction time 30 min) in a dry solvent (total volume 4 ml) Nitrone (1 0 mmol) was added at room temperature followed by ethyl vinyl ether (3 equiv) After 5-24 hrs the reaction mixture was quenched with saturated aqueous bicarbonate, extracted

with dichloromethane and diethyl ether, dried with Na_2SO_4 and concentrated under vacuum to give the crude 5-ethoxyisoxazolidine Samples (*ca* 10 mg) for HPLC analysis were purified by flash chromatography on silica gel using ether/*n*-hexane (1/1-4, v/v) as eluent followed by concentration under vacuum

B High-pressure and chiral oxazaborolidine catalyzed 1,3-dipolar cycloaddition of nitrones with ethyl vinyl ether (General procedure)

The reaction mixture (2 ml), prepared according to A, was placed into a 1 5 ml teflon ampule flushed with dry argon The ampule was closed and kept under 1-4 kbar pressure for the reported time After depressuring, the reaction mixture was worked up as usual (Procedure A)

C Chiral oxazaborolidine catalyzed 1,3-dipolar cycloaddition of pyrroline N-oxide **4** with 2,3-dihydrofuran **5** (General procedure)

The chiral oxazaborolidines (0 2 mmol) were prepared *in situ* at room temperature under an inert nitrogen atmosphere from N-arylsulphonyl-*L*-α-amino acids[3] by addition of equimolar amounts of BH_3 THF (1M solution in THF) or phenyl- or *n*-butylboronic acid (in the presence of 4Å powdered molecular sieves) in 2,3-dihydrofuran **5** (total volume 4 ml) Nitrone **4** (1 0 mmol) was added at room temperature After 5-24 hrs the reaction mixture was quenched with saturated aqueous bicarbonate, extracted with dichloromethane and diethyl ether, dried with Na_2SO_4 and concentrated under vacuum to give the crude *exo*-isoxazolidine **6** Samples for chiral HPLC analysis were purified as described under A

5-Ethoxy-3-phenyl-N-methyl isoxazolidine 3[5a]

All physical data were identical to those reported in the literature[5a] HPLC analysis on Daicel Chiralcel OD column, eluent *n*-hexane/2-propanol (98/2, v/v) , flow rate 1 0 ml/min , UV detection at 226 nm, *cis* isomers 4 71 and 8 80 min , *trans* isomers 6 77 and 9 48 min

5-Ethoxy-3-phenyl-N-benzyl isoxazolidine 13

cis Isomer **13** oil, ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 1 21 3H, t, J = 7 1 Hz, CH_2CH_3, 2 31 1H, m, H-4, 2 88 1H, m, H-4, 3 47 1H, dq, J = 7 1 Hz and J = 9 3 Hz, CHH-CH_3, 3 65 2H, d, J = 14 7 Hz, CH_2-Ph, 3 77 1H, dq, J = 7 1 Hz and J = 9 3 Hz, CHH-CH_3, 4 02 1H, d, J = 14 8 Hz, H 3, 5 17 1H, dd, J = 3 0 Hz and J = 6 3 Hz, H-5, 7 19-7 49 10H, m, ArH ^{13}C-NMR δ (ppm) 15 2 (CH_3), 46 7 (C-4), 59 1 (CH_2-CH_3), 63 4 (CH_2-Ph), 70 4 (C-3), 100 7 (C-5), 126 8-129 6 (10 C Ar), 137 7 (C_{ipso}, N-aryl), 138 6 (C_{ipso}, 3-phenyl) HRMS m/e (rel int) $C_{18}H_{21}NO_2$ 284 (M+1, 2), 283 (M+, 12), 162 (12), 161 (96), 133 (25), 115 (3), 105 (15), 91 ($PhCH_2^+$, 100) Peak Match Calc 283 1572 Found 283 1578 ± 0 0011

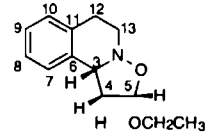
trans isomer **13** oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1 26 3H, t, J = 7 1 Hz, CH_2CH_3, 2 45 1H, ddd, J = 4 9, 10 2 and 12 7 Hz, H-4, 2 62 1H, dd, J = 6 4 and 12 7 Hz, H-4, 3 48 1H, dq, J = 7 1 Hz and J = 9 5 Hz, CHH-CH_3, 3 86 1H, dq, J = 7 1 and 9 5 Hz, CHH-CH_3, 4 08 2H, d, J = 2 9 Hz, CH_2-Ph , 4 31 1H, dd, J = 6 4 and 10 2 Hz, H-3, 5 19 1H, d, J = 4 9 Hz, H-5, 7 19-7 44 10H, m,

ArH ^{13}C-NMR δ (ppm) 15 2 (CH_3), 46 1 (C-4), 62 9 ($\underline{C}H_2$-CH_3), 63 6 ($\underline{C}H_2$-Ph), 67 9 (C-3), 102 5 (C-5), 127 0-129 4 (10 C-Ar), 138 0 (C_{ipso}, N-aryl), 140 0 (C_{ipso}, 3-phenyl) HRMS m/e (rel int) $C_{18}H_{21}NO_2$ 284 (M+1, 3), 283 (M+, 12), 213 (4), 162 (12), 161 (95), 133 (24), 115 (4), 105 (14), 91 ($PhCH_2^+$, 100) Peak Match Calc 283 1572 Found 283 15778 ± 0 00084 HPLC analysis on Daicel Chiralcel OD column, eluen 98/2 (v/v) *n*-hexane/2-propanol, flow rate 1 0 ml/min , UV detection at 226 nm, cis isomers 4 45 and 9 09 min , trans isomers 5 97 and 7 17 min

5-Ethoxy-3-phenyl-N-phenyl isoxazolidine <u>14</u>[11]

All physical data were identical to those reported in the literature[11] The enantiomeric mixture of *cis* and *trans*-**<u>14</u>** could not be separated by HPLC using a Daicel Chiralcel OB, OD or Chiralpak AD column, eluent 90/10 99/1 (v/v) *n* hexane/2-propanol, flow rate 0 75-1 0 ml/min , UVdetection at 226 nm

5-Ethoxy-isoxazolidine <u>15</u>

atom numbering 

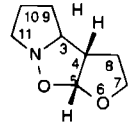
cis-Isomer **<u>15</u>** oil, ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 1 25 3H, t, J = 7 1 Hz, CH_3, 2 44 1H, ddd $J_{H4\,H3}$ = 7 4 Hz, $J_{H4\,H5}$ = 5 4 Hz, $J_{H4\,H4}$ = 13 4 Hz, H-4, 2 65 1H, ddd, $J_{H4\,H3}$ = 7 4 Hz, $J_{H4\,H4}$ = 13 4 Hz, $J_{H4\,H5}$ = 0 Hz, H-4 , 2 88 2H, m, H-12, H-12 , 3 20 1H, ddd, $J_{H13\,H12}$ = 7 5 Hz, $J_{H13\,H12}$ = 4 7 Hz, $J_{H13\,H12}$ = 11 1 Hz, H-13', 3 31 1H, ddd, $J_{H13\,H12}$ = 5 4 Hz, $J_{H13\,H12}$ = 5 7 Hz, $J_{H13\,H13}$ = 11 1 Hz, H 13, 3 49 1H, dq, J = 7 1 Hz, J = 2 3 Hz, diastereotope H_a, 3 86 1H, dq, J = 7 1 Hz J = 2 3 Hz, diastereotope H_b, 4 76 1H, t, $J_{H3\,H4}$ = 7 4 Hz, H-3, 5 26 1H, d, $J_{H5\,H4}$ = 5 4 Hz, H 5 7 15 4H, arom H ^{13}C-NMR δ (ppm) 15 1 (CH_3) 26 8 (CH_2, C-12), 43 5 (CH_2, C-4), 49 6 (CH_2, C-13), 60 1 (C-3), 63 2 (CH_2O), 101 6 (C-5), 126 4 (C-8), 126 4 (C-9), 128 2 (C-7), 133 8 (C 11), 135 7 (C-6) HRMS m/e (rel intensity) $C_{13}H_{17}NO_2$ 219 (M^+, 15), 174 (-OEt, 6), 148 (19), 147 (100), 130 (18), 117 (17) Peak Match Calc 219 2593 Found 219 2600 ± 0 00066

trans-Isomer **<u>15</u>** oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1 18 3H, t, J = 7 1 Hz, CH_3, 2 35 1H, ddd, $J_{H4\,H3}$ = 10 2 Hz, $J_{H4\,H5}$ = 3 9 Hz, $J_{H4\,H4}$ = 11 6 Hz, H-4, 2 78 1H, d, J = 16 3 Hz, 2 96 1H, ddd, J = 6 6 Hz, J = 1 7 Hz, J = 9 6 Hz, H-4 , 3 06 1H, ddd, $J_{H13\,H12}$ = 6 8 Hz, $J_{H13\,H12}$ = 4 7 Hz, $J_{H13\,H12}$ = 11 1 Hz, H-13 , 3 39 1H, m, H-13, 3 54 2H, m, diastereotope H_a and H-13 , 3 84 1H, dq, J = 7 1 Hz, J = 2 3 Hz, diastereotope H_b, 4 58 1H, t, $J_{H3\,H4}$ = 9 6 Hz, H-3, 5 36 1H, dd, $J_{H5\,H4}$ = 3 9 Hz, $J_{H5\,H4}$ = 6 6 Hz, H-5, 7 14 4H, arom -H ^{13}C-NMR δ (ppm) 15 2 (CH_3), 29 5 (CH_2, C-12), 44 2 (CH_2, C-4), 49 9 (CH_2, C-13), 62 5 (C-3), 64 0 (CH_2O), 106 1 (C-5), 126 2 (C-9), 126 5 (C 8), 127 5 (C-7), 133 4 (C-11), 135 6 (C-6) HPLC analysis on Daicel Chiralcel OD column, eluent 95/5 (v/v)*n*-hexane/2-propanol, flow rate 1 0 ml/min , UV detection at 226 nm, *cis* isomers 7 17 and 14 90 min *trans* isomers 8 53 and 8 97 min

5-Ethoxy-3-benzoyl-N-phenyl isoxazolidine 17[13]

cis-Isomer **17** oil, ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 1 23 3H, t, J = 7 1 Hz, CH_3, 2 67 1H, ddd, J = 1 7, 5 1 and 14 Hz, H-4, 2 90 1H, ddd, J = 5 8, 10 0 and 14 Hz, H-4, 3 58 1H, dq, J = 7 1 and 9 5 Hz, diastereotope C*H*H-CH_3, 3 95 1H, dq, J = 7 1 and 9 5 Hz, diastereotope CH*H*-CH_3, 4 65 1H, dd, J = 5 7 and 10 0 Hz, H-3, 5 42 1H, dd, J = 1 7 and 5 8 Hz, H-5, 6 98-7 25 5H, m, N-ArH, 7 45-8 20 5H, ArH ^{13}C-NMR δ (ppm) 15 0 (CH_3), 40 6 (CH_2), 63 7 (O$\underline{C}H_2$), 71 5 (C-3), 100 7 (C-5), 116 0 (C-Ar), 122 8 (C-Ar), 128 4 (C-Ar), 129 4 (C-Ar), 133 3 (C-Ar), 135 0 (C_{ipso}, Ar), 150 1 (C_{ipso}, N-Ar), 196 9 (C=O) HRMS m/e (rel int) $C_{18}H_{19}NO_3$ 298 (M+1, 1), 297 (M+, 5), 193 (12), 192 ($C_6H_5CO^+$, 100), 146 (8), 135 (4), 118 (22), 105 (37) Peak Match Calc 297 1365 Found 297 13661 ± 0 00088 HPLC analysis on Daicel Chiralcel OD column, eluent 90/10 (v/v) *n*-hexane/2-propanol, flow rate 0 75 ml/min , UV detection at 226 nm, *cis* isomers 9 31 and 10 26 min

1-Aza-2,4-dioxatricyclo[6.3.0.0]undecane 6[5c]

atom numbering 

Oil, ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 1 70 2H, m, H-10, 1 94-2 09 4H, m, H-8 and H-9, 2 95 1H, m, H-4, 3 11 1H, dd, J = 6 0 and 7 5 Hz, H-7, 3 34 1H, t, J = 8 0 Hz, H-7, 3 48 1H, m, H-11, 3 95 1H, m, H-11, 4 13 1H, ddd, J = 6 0, 8 2 and 10 7 Hz, H-3, 5 71 1H, d, J = 5 2 Hz, H-5 ^{13}C NMR δ (ppm) 24 0 (CH_2, C-10), 31 2 (CH_2, C-8), 32 5 (CH_2, C-9), 54 0 (C-4), 57 0 (CH_2, C-7), 68 5 (CH_2, C-11), 73 7 (C-3), 106 2 (C-5) All ^{1}H-NMR data were in full agreement with the data reported in the literature[5c] HRMS m/e (rel int) $C_8H_{13}NO_2$ 156 (M+1, 1), 155 (M+, 13), 110 (5), 96 (9), 87 (5), 86 (100), 70 (9) Peak Match Calc 155 0946 Found 155 0949 ± 0 00062 HPLC analysis on Daicel Chiralpak AD column, eluent 98/2 (v/v) *n*-hexane/2-propanol, flow rate 0 75 ml/min , UV detection at 210 nm, isomers 28 9 and 30 3 min

5.5 References and Notes

1 a) Tufariello, J J In *1,3-Dipolar Cycloadditions Chemistry*, Padwa, A , Ed , Wiley, New York, **1984**, vol 2, pp 83-168, b) Confalone, P N , Huie, E M *Org React* **1988**, *36*, 1-173, c) Balasubramanian, N *Org Prep Proc Int* **1985**, 25, d) Black, D S , Crozier, R F , Davis, V C *Synthesis*, **1975**, 205-221, e) Annunziata, R , Cinquini, M , Cozzi, F , Raimondi, L *Gazz Chim Ital* **1989**, *119*, 253-269, f) Mulzer, J *Nachr Chem Tech Lab* **1984**, *32*, 882-887, g) Torssell, K B G *Nitrile Oxides, Nitrones, and Nitronates in Organic Synthesis*, VCH Weinheim, **1988**, pp 1-47, 75-89, 129-327, h) Dopp, D , Dopp, H in 'Houben Weyl-Methoden der Organischen Chemie", vol E14b, Klamann, D , Hagemann, H , Eds , Georg Thieme Verlag Stuttgart, **1990**, i) Grunanger, P , Vita-Finzi, P "The Chemistry of Heterocyclic Compounds", Taylor, E C , Ed , Vol 49, Part 1, John Wiley & Sons, New York,

1991, Chapter 3 Isoxazolidines , p 705

2 a) Murahashi, S -I , Imada, Y , Kohno, M , Kawakami, T *Synlett*, **1993**, 395-396 (ref 2 and 3 cited therein), b) Mukai, C , Kim, I J , Cho, W J , Kido, M , Hanaoka, M *J Chem Soc Perkin Ttrans I* **1993**, 2495-2503, c) Murahashi, S -i , Sun, J , Tsuda, T *Tetrahedron Lett* **1993**, *34*, 2645 2648, d) Goti, A , Cicchi, S , Brandi, A , Pietrusiewitz, K M *Tetrahedron Asymmetry* **1991**, *2*, 1371-1378, e) Takahashi, T , Fujii, A , Sugita, J , Hagi, T , Kitano, K , Arai, Y , Koizumi, T , Shiro, M *Tetrahedron Asymmetry* **1991**, *2*, 1379-1390, f) Brandi, A , Cicchi, S , Goti, A , Koprowski, M , Pietrusiewicz, K M *J Org Chem* **1994**, *59*, 1315-1318, g) Wovkulich, P M , Baggiolini, E G , Hennessy, B M , Uskokovic, M R *Heterocycles* **1993**, *35*, 791 797, h) Tamura, O , Yamaguchi, T , Noe, K , Sakamoto, M *Tetrahedron Lett* **1993**, *34*, 4009-4010, i) Tamura, O , Yamaguchi, T , Okabe, T , Sakamoto, M *Synlett* **1994**, 620-622, j) Konosu, T , Oida, S *Chem Pharm Bull* **1993**, *41*, 1012-1018, k) Keller, E , de Lange, B , Rispens, M T , Feringa, B L *Tetrahedron* **1993**, *49*, 8899-8910, Rispens, M T , Keller, E , de Lange, B , Zijlstra, R W J , Feringa, B L *Tetrahedron Asymmetry* **1994**, *5*, 607-624, l) Gravestock, M B , Knight, D W , Lovell, J S , Thornton, S R *J Chem Soc Perkin Trans I* **1994**, 1661-1663, m) Saito, S , Ishikawa, T , Moriwake, T *J Org Chem* **1994**, *59*, 4375-4377, n) Naito, T , Ikai, M , Shirakawa, M , Fujimoto, K , Ninomiya, I , Kiguchi, T *J Chem Soc Perkin Trans I* **1994**, 773-775, o) Aurich, H G , Quintero, J -L R *Tetrahedron* **1994**, *50*, 3929-3942, p) Ishizuka, T , Matsunaga, H , Iwashita, J , Arai, T , Kunieda, T *Heterocycles* **1994**, *37*, 715-718

3 a) Scarpati, R , Sica, D , Santacroce, C *Gazz Chim Ital* **1966**, *96*, 375-386, b) Huisgen,R , Grashey, R , Seidl, H , Hauck, H *Chem Ber* **1968**, *101*, 2559-2563, c) Keirs, D , Moffat, D , Overton, K , Tomanek, R *J Chem Soc Perkin Trans I* **1991**, 1041 1051, d) Seerden, J P G , Scholte op Reimer, A W A , Scheeren, J W *Tetrahedron Lett* **1994**, *35*, 4419-4422, e) Chapters 3 and 4 of this thesis, f) for reviews on chiral Lewis acid catalyzed reactions see Narasaka, K *Synthesis* **1991**, 1-11, Kagan, H B , Riant, O *Chem Rev* **1992**, 1007-1019, Lohray, B B , Bhushan, V *Angew Chem* **1992**, *104*, 740-741, Wallbaum, S , Martens, J *Tetrahedron Asymmetry* **1992**, *3*, 1475-1504, Deloux, L , Srebnik, M *Chem Rev* **1993**, *93*, 763-784

4 Ketene silyl acetals react with nitrones to give silyl group transfer reactions under Lewis acid ($ZnCl_2$) catalyzed conditions, see Tomoda, S , Takeuchi, Y , Nomura, Y *Chem Lett* **1982**, 1787-1790, Kita, Y , Itoh, F , Tamura, O , Ke, Y Y , Tamura, Y *Tetrahedron Lett* **1987**, *28*, 1431-1434, Kita, Y , Tamura, O , Itoh, F , Kishino, H , Miki, T , Kohno, M , Tamura, Y *J Chem Soc Chem Commun* **1988**, 761-763

5 a) Dicken, C M , DeShong, P *J Org Chem* **1982**, *47*, 2047-2051, Dicken, C M , DeShong, P , Staib, R R , Freyer, A J , Weinreb, S M *J Org Chem* **1982**, *47*, 4397, b) For application in amino sugar synthesis see DeShong, P , Leginus, J M *J Am Chem Soc* **1983**, *105*, 1686-1688, DeShong, P , Dicken, C M , Leginus, J M , Whittle, R R *J Am Chem Soc* **1984**, *106*, 5598-5602, c) Iwashita, T , Kusumi, T , Kakisawa, H *Chem Lett* **1979**, 1337-1340, Iwashita, T , Kusumi, T , Kakisawa, H *J Org Chem* **1982**, *47*, 230-233, d) Huisgen,

R , Grashey, R , Seidl, H , Hauck, H *Chem Ber* **1968**, *101*, 2559-2567, e) Bravo, P , Bruché, L , Farina, A , Fronza, G , Meille, S V , Merli, A *Tetrahedron Asymmetry* **1993**, *4*, 2131-2134

6 The corresponding silyl enol ethers are reported to give a regioselective TMSOTf-catalyzed [3+2]-cycloaddition with nitrones affording 5-silyloxyisoxazolidines with poor endo/exo stereoselectivity, see Dhavale, D D , Trombini, C *J Chem Soc , Chem Commun* **1992**, 1268-1270, Camiletti, C , Dhavale, D D , Gentilucci, L , Trombini, C *J Chem Soc Perkin Trans I* **1993**, 3157-3165, Camiletti, C , Poletti, L , Trombini, C *J Org Chem* **1994**, *59*, 6843-6846

7 a) Houk, K N , Sims, J , Duke, Jr , R E , Strozier, R W , George, J K *J Am Chem Soc* **1973**, *95*, 7287-7301, b) Houk, K N , Sims, J , Watts, C R , Luskus, L J *J Am Chem Soc* **1973**, *95*, 7301-7315, c) Pascal, Y L , Chanet-Ray, J , Vessiere, R , Zeroual, A *Tetrahedron* **1992**, *48*, 7197-7208

8 Leonard, N J , Saba, T *J Org Chem* **1969**, *34*, 1066, Brandange, S , Lundin, C *Acta Chem Scand* **1971**, *25*, 2447, Visconti, M, Gillhof-Schaufelberger, H *Helv Chim Acta* **1971**, *54*, 449, Visconti, M , Buzek, H *Helv Chim Acta* **1972**, *55*, 670, Pizzorno, M T , Albonico, S M *J Org Chem* **1974**, *39*, 731, Lown, J W , Itoh, T *Can J Chem* **1975**, *53*, 960, Tufariello, J J , Tette, J P *J Org Chem* **1975**, *40*, 3866, Stevens, R V , Luh, Y , Sheu, J -T *Tetrahedron Lett* **1976**, 3799, Borch, R F , Ho, B C *J Org Chem* **1977**, *42*, 1225, Danishefsky, S , McKee, R , Singh, R K *J Am Chem Soc* **1977**, *99*, 4783, Pinnick, H W , Chang, Y -H *J Org Chem* **1978**, *43*, 4662, Pinnick, H W , Chang, Y -H *Tetrahedron Lett* **1979**, 837

9 F L Warren in "The Alkaloids-Chemistry and Physiology ', Vol XII, R H F Manske, Ed , Academic Press, New York, **1970**, p 319, D H G Croat in "The Alkaloids ', Vol VI, The Chemical Society, London, **1976**, p 84

10 a) Yoshimura, Y , Osugi, J , Nakahara, M *J Am Chem Soc* **1983**, *105*, 5415-5418, b) For a recent example of application of high pressure to 1,3-dipolar cycloaddition of nitrones see Ahn, C , Kennington, Jr , J W , DeShong, P *J Org Chem* **1994**, *59*, 6282-6286, c) Tietze, L F , Ott, C , Gerke, K , Buback, M *Angew Chem Int Ed Engl* **1993**, *32*, 1485-1486

11 Paul, R , Tchelitcheff, S *Bull Soc Chim France* **1967**, 4179-4183

12 a) Huisgen, R , Wulff, J *Chem Ber* **1969**, *102*, 1848-1858, b) Niwayama, S , Dan, S , Inouye, Y , Kakisawa, H *Chem Lett* **1985**, 957-960, c) Inouye, Y , Niwayama, S , Okada, T , Kakisawa, H *Heterocycles* **1987**, *25*, 109-111, d) Kanemasa, S , Tsuruoka, T , Wada, E *Tetrahedron Lett* **1993**, *34*, 87-90, e) Armstrong, S K , Collington, E W , Stonehouse, J , Warren, S *J Chem Soc Perkin Trans I*, **1994**, 2825-2831

13 Barton, D H R , Bolton, M , Magnus, P D , Marathe, K G , Poulton, G A , West, P J *J Chem Soc Perkin I*, **1973**, 1574-1579 Although the reported yield of the crude product is 85%, we could isolate under exactly the same conditions only 27% yield of cycloadduct **17**

14 Recently, Mukai *et al* reported that the general lack of stereocontrol observed in these reactions with ethyl vinyl ether can be overcome by using chromium complexed nitrones

The *endo* stereoselectivity of the cycloaddition with ethyl vinyl ether was controlled by the introduction of the tricarbonylchromium moiety onto the benzene ring The corresponding *cis*-adducts were obtained exclusively in good yields Mukai, C , Kim, I J , Cho, W J , Kido, M , Hanaoka, M *J Chem Soc Perkin Trans I*, **1993**, 2495-2503

15 Aben, R W M , Scheeren, J W *J Org Chem* **1987**, *52*, 365

16 General procedures for the synthesis of N-benzyl nitrones are a) The reaction of carbonyl compounds with hydroxylamines Dondoni, A , Franco, S , Junquera, F , Merchán, F , Merino, P , Tejero, T *Synth Commun* **1994**, *24*, 2537-2550; b) Catalytic oxidation of *N,N*-disubstituted hydroxylamines with NMO/TPAP Goti, A , De Sarlo, F , Romani, M *Tetrahedron Lett* **1994**, *35*, 6571-6574, c) Oxidation of secondary amines ref 17

17 Murahashi, S -I , Shiota, T , Imada, Y *Org Synth Vol 70*, **1992**, 265-271, Murahashi, S -I , Mitsui, H , Watanabe, T , Zenki, S -i *Tetrahedron Lett* **1983**, *24*, 1049-1052

18 a) Sasaki, T , Mori, K , Ohno, M *Synthesis* **1985**, 279-280, b) Johnson, A W , Amel, R T *J Org Chem* **1969**, *34*, 1240-1247, c) ref 1h, pp 1401, 1488

19 The sulfonamides were prepared from commercially available amino acids and derivatives according to Houben-Weyl, *'Methoden der Organischen Chemie'*, Band 15/1, *Synthese von Peptiden* I, 4^{e}Auflage, Georg Thieme Verlag, Stuttgart, **1974**, pp 223-233 Under these conditions no racemisation of the sulfonamides has been reported

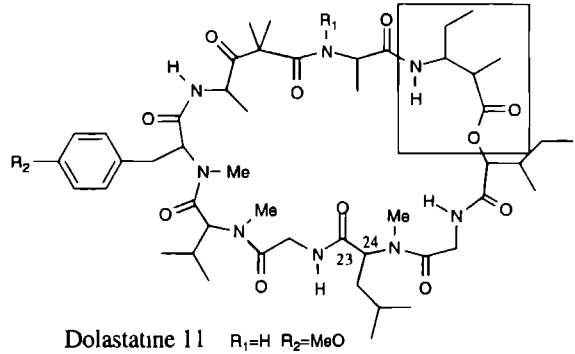
20 Heathcock, C H , Davidsen, S K , Hug, K T , Flippin, L A *J Org Chem* **1986**, *51*, 3027

CHAPTER 6

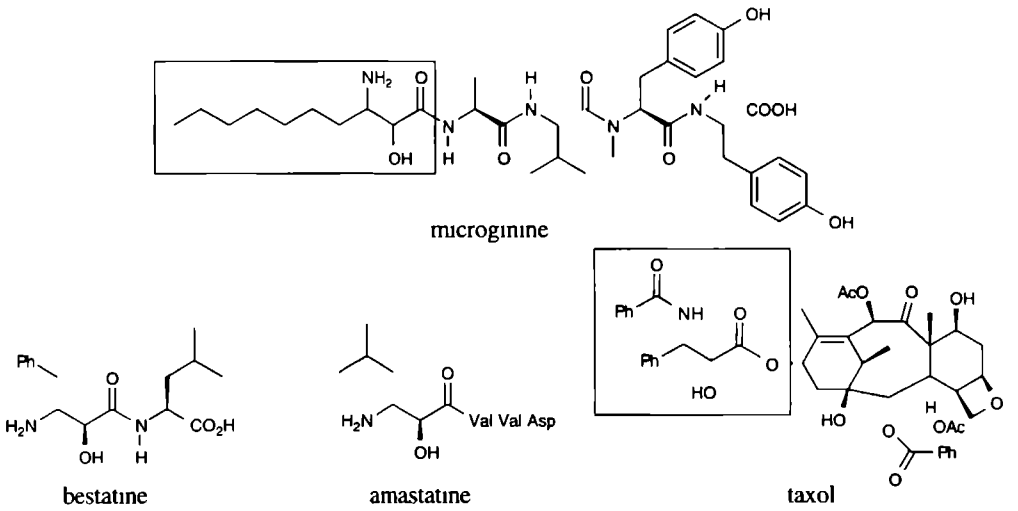
Asymmetric Synthesis of β-Amino Esters via Chiral 5,5-Dialkoxyisoxazolidines

6.1 Introduction

The interesting farmacological properties[1] of naturally occurring β-amino acids and the ability to cyclize β-amino acids to β-lactams[2], a well-known class of potentially biologically active natural substances, have stimulated the development of new methods for the asymmetric synthesis of these compounds[3] β-Amino acids are sometimes also components of naturally occurring biologically active peptides For example, 3-amino-2-methylpentanoic acid[4] is present in the structurally related antifungal depsipeptides, majusculamide C[5a] and 57-nor-majusculamide C[5b], and the antitumor agents, dolastatins 11 and 12[5c] Various peptidic enzyme inhibitors such as microginine[6] (angiotensin-converting enzyme inhibitor), bestatine and amastatine[7] (antitumor and antimicrobial activity), and the norstatine family[8] (renine and HIV protease inhibitors) contain α-hydroxy β-amino acids Taxol® (paclitaxel), a complex diterpene containing a (-)-N-benzoyl-(*2R,3S*)-3 phenylisoserine side chain[8a,9], is currently the most outstanding lead compound for cancer chemotherapy Although the natural reserves of taxol are limited, the taxol precursor 10-deacetyl baccatin which lacks the β-amino acid side chain is readily available from the leaves of several *Taxus* species It has been shown that the β-amino acid side chain is necessary for biological activity These findings have sparked interest in the synthesis of α-hydroxy-β-amino acids

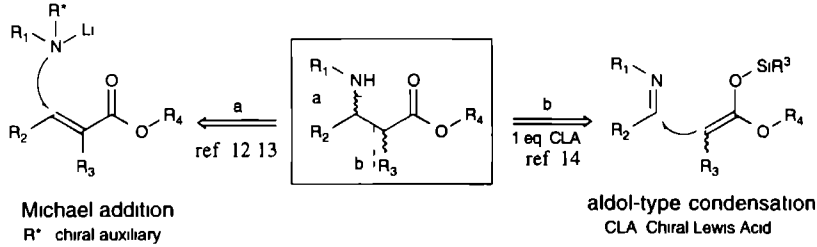


Dolastatine 11 R_1=H R_2=MeO
Dolastatine 12 R_1= Me R_2= H
Majusculamide C R_1=H R_2=MeO, C-23 24 ILe



Several methods have been developed for the preparation of homochiral or enantio-enriched β-amino acids They are mostly based on the chiral auxiliary strategy or on the diastereoselective and chemoselective elaboration of chiral starting materials[3,10] The need for efficient methodologies where asymmetric induction is achieved in a catalytic fashion[11] is thus clearly apparent The most important C-N and C-C bond forming methods (> 95% de or ee) are the diastereoselective Michael addition of chiral lithium amides, as chiral ammonia equivalents, to α,β-unsaturated esters[12 13] and the chiral Lewis acid catalyzed asymmetric addition of ketene silyl acetals to (chiral) imines[14] (*Scheme 1*) Both methods have been optimized for various substituents to proceed with quantitative diastereo and enantioselectivity However, for reasons of *atom economy* there are some disadvantages First, the asymmetric Michael addition approach consumes a stoichiometric amount of of chiral auxiliary to be incorporated in the Michael adduct The chiral auxiliary, i e the α-methylbenzyl group[12], is subsequently removed by hydrogenolysis over Pd/C and therefore can not be recovered

Scheme 1 Some strategies for the asymmetric synthesis of β-amino esters

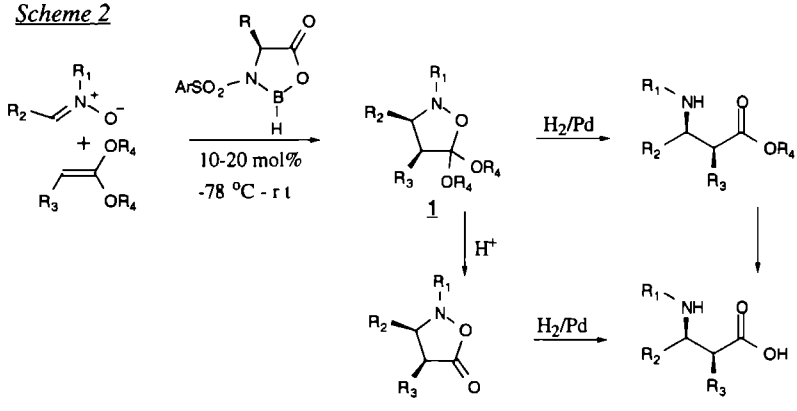


The asymmetric aldol-type addition of ketene silyl acetals to chiral imines is catalyzed by stoichiometric amounts (1 2 equiv) of a chiral Lewis acid derived from the expensive compound *R*- or *S*-BINOL This double diastereo-differentiating reaction was adapted to an enantioselective

version by use of N-benzhydryl imines and a chiral Brønsted acid-assisted chiral Lewis acid Although the chiral ligand can be recovered the expensive trialkylsilyl group is lost during work-up of the reaction Eventually, the (chiral) N-protecting groups (e g benzhydryl, α-methylbenzyl) are removed by hydrogenolysis over Pd/C

The synthesis of isoxazolidines via 1,3-dipolar cycloaddition of nitrones to olefins has been extensively reported and several excellent reviews have appeared[15] The ever-increasing use of isoxazolidine derivatives as important intermediates in the multistep synthesis of complex natural products is based on some obvious advantages of this heterocyclic ring 1) the remarkable regio- and stereoselectivities of both inter- and intramolecular cycloadditions of nitrones to olefinic compounds, 2) the ease of ring opening either by hydrogenolysis or by thermolytic and oxidative processes, and 3) the numerous possibilities for recyclization of the ring-opened product, usually arising from the nitrogen atom nucleophilicity and from a suitable substitution pattern in either position 5 or 4 of the original isoxazolidine ring Up to now the synthetic utility of isoxazolidine intermediates has been evidenced mainly in the field of alkaloids although some applications in other areas of natural products are also known

Scheme 2

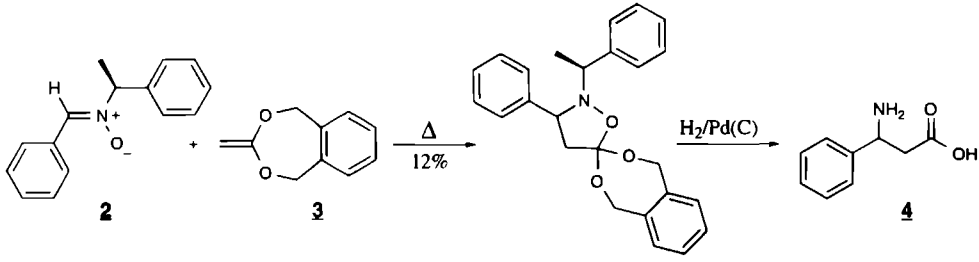


The 1,3-dipolar cycloaddition of nitrones with ketene O,O-dialkylacetals proceeds under thermal conditions at elevated temperatures[16a-c] or at low temperatures, but in that case catalyzed by Lewis acids[16d] e g chiral oxazaborolidines, to afford 5,5-dialkoxyisoxazolidines **1**, which can be considered as versatile intermediates for the preparation of β-amino esters and acids (Scheme 2)[16c,d] The latter compounds may be prepared by acidic or basic hydrolysis of the corresponding esters obtained by catalytic hydrogenation of the N-O bond or by acidic hydrolysis of the 5,5 dialkoxyisoxazolidines to the corresponding isoxazolidinones followed by hydrogenation of the N-O bond In this chapter the synthetic applications of 5,5-dialkoxyisoxazolidines **1** are investigated, especially aimed at the synthesis of β-amino esters

Cleavage of the N-O bond in isoxazolidines, in both the free base and the quaternary salts, is easily promoted by a large variety of reducing agents The catalytic hydrogenation is quite general both with monocyclic, bicyclic or polycyclic isoxazolidines, and excellent yields are usually achieved with Raney nickel, platinum oxide, Pd/C, Rh/C, aluminium amalgam in THF/H_2O, diborane,

titanium trichloride in refluxing ethanol, and zinc in combination with acetic acid[17] Since the hydrogenolysis reaction is stereospecific, conclusions concerning the stereochemistry of the isoxazolidine derivative can be drawn The use of 5,5-dialkoxyisoxazolidines as versatile intermediates for β-amino acids has recently been demonstrated by Keirs *et al* [16c] (*Scheme 3*)

Scheme 3



2 **3** **4**

The 1,3-dipolar cycloaddition of chiral nitrone **2** and *o*-xylylene ketene acetal **3** proceeds under classical thermal heating to give the cycloadduct with moderate diastereoselectivity (60% ee) Subsequent hydrogenolysis of the cycloadduct affords the chiral β-amino acid **4** in low yield (12%)

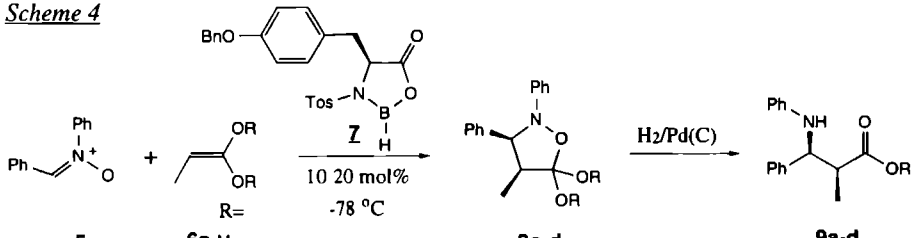
6.2 Results and discussion

6.2.1 Catalytic hydrogenation of 5,5-dialkoxyisoxazolidines

In Chapters 3 and 4 of this thesis it was reported that the asymmetric 1,3-dipolar cycloaddition of C,N-diphenylnitrone **5** with 1,1-dialkoxypropenes **6a-d** is catalyzed by catalytic amounts of chiral oxazaborolidines **1** at -78 °C to give regioselectively and stereoselectively *cis*-2,3-diphenyl-4-methyl-5,5-dialkoxyisoxazolidines **8a-d** The best enantioselectivities were obtained with chiral oxazaborolidine **7** derived from the tosylamide of *L*-tyrosine(O-benzyl ether) With this catalyst both enantiomers of isoxazolidine **8b** have been prepared by varying the solvent composition

The *cis*-2,3-diphenyl-4-methyl-5,5-dialkoxyisoxazolidines **8a-d** could be quantitatively converted to the corresponding *syn*-β-amino esters **9a-d** by hydrogenolysis with 1 atm H_2 on Pd(C) in ethanol at room temperature (*Scheme 4*)

Scheme 4

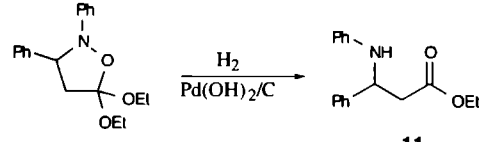


5 **6a** Me **6b** Et **6c** *n* Pr **6d** *i*-Pr **8a-d** **9a-d**

The ^{1}H NMR spectra of the *syn*-β-amino esters **9a-d** all displayed a doublet signal for H-3 at *ca* 4 7 ppm with a coupling constant of *ca* 5 Hz Hydrogenolysis of the crude isoxazolidine **8d** afforded a 85/15 mixture of the *syn*-β-amino ester **9d** and its *anti* isomer (coupling constant of the doublet signal for H-3 is 7 Hz)

Under the same hydrogenolysis conditions 2,3-diphenyl-5,5 diethoxyisoxazolidine **10**, prepared from C,N-diphenylnitrone and 1,1-diethoxyethene, gave no clean reaction but afforded a mixture of β-amino ester **11** and some smaller fragments due to hydrogenolysis of the internal N benzylic bond With $Pd(OH)_2/C$ as a catalyst and 1 atm of hydrogen pressure β-amino ester **11** was obtained as the exclusive product with identical physical data as reported in the literature (*Scheme 5*)[18]

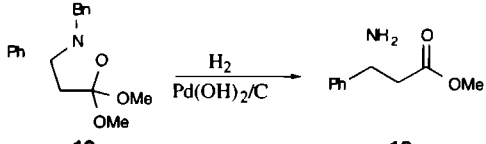
Scheme 5



10 **11**

In general, the stereoselective preparation of α-alkylated β amino acids or esters via the usual procedures, e g Michael-type additions, is rather difficult[4 12f 12g 13f] In contrast, the 1,3-dipolar cycloaddition of nitrones with 1,1-dialkoxypropenes provides a high-yield synthetic route to *syn*-α-methyl-β-amino esters The chiral oxazaborolidine catalyzed 1,3-dipolar cycloaddition of N-benzyl nitrones[19] with ketene acetals is of particular interest for the synthesis of chiral β-amino esters because hydrogenolysis of the resulting N benzyl isoxazolidine, e g **12**, leads in one step to the *syn* β-amino ester **13** with a free amino group Optimal conditions for conversion of the N-benzyl isoxazolidine **12** into β-amino ester **13** were achieved by hydrogenolysis with $Pd(OH)_2/C$ and 1 atm of hydrogen pressure (*Scheme 6*)

Scheme 6



12 **13**

This methodology was further applied to the synthesis of *syn*-2-methyl-3-aminopentanoate **17**[4], a component of various natural products, e g majusculamide C, dolastatins 11 and 12 The 1,3-dipolar cycloaddition reaction of C-ethyl-N-benzyl nitrone **14**[20] with 1,1-dimethoxypropene was catalyzed by 20 mol% of chiral oxazaborolidines **15** at -78 °C to give regio- and stereoselectively the N benzyl-5,5-dimethoxyisoxazolidine **16**, which was immediately converted to the β-amino ester **17** via hydrogenolysis with 1 atm H_2 and $Pd(OH)_2/C$ as catalyst (*Scheme 7* Table 1) The nitrone **14** and the isoxazolidine **16** are not stable and the best results were obtained when the 1,3-dipolar cycloaddition reaction of freshly prepared nitrone with ketene acetal was immediately followed by hydrogenolysis Isolated yields up to 77% were obtained after two steps

Scheme 7

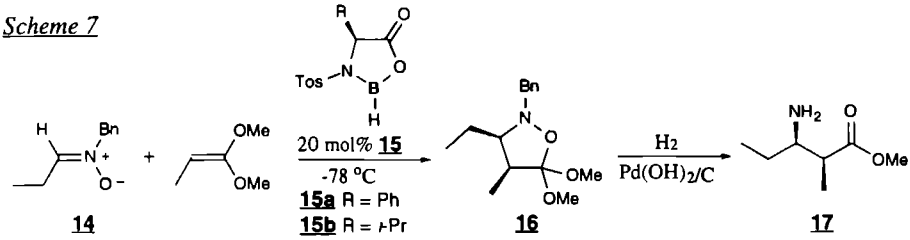


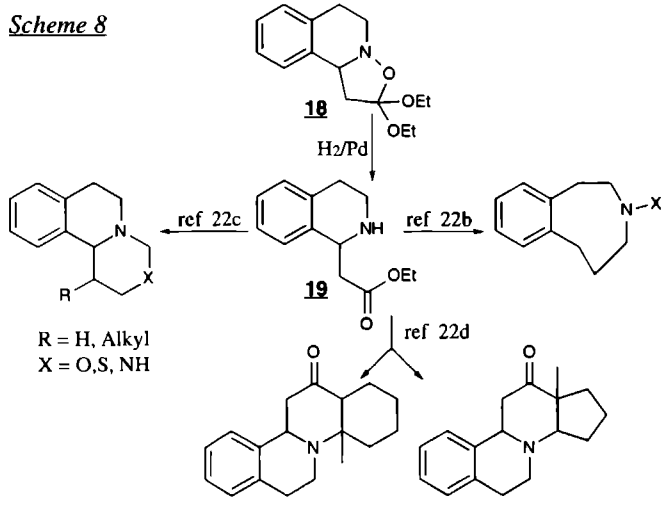
Table 1 Catalytic asymmetric synthesis of methyl 2-methyl-3-aminopentanoate **17** from nitrone **14** and 1,1-dimethoxypropene

entry	catalyst	starting borane	solvent	e e **17** (%)
1	**15a**	BH_3-THF in THF	CH_2Cl_2	15
2	**15a**	BH_3-SMe_2 in toluene	toluene	12
3	**15b**	BH_3-THF in THF	CH_2Cl_2	16

The enantiomeric excess of **17** was determined by HPLC using a chiral Daicel Chiralcel OD column GC analysis of the corresponding diastereomeric Mosher-amides gave similar results Remarkably, the low enantioselectivity (entry 1) was not improved by changing the solvent composition from dichloromethane/THF to toluene (entry 2) It has been previously shown that the solvent had a dramatical influence on the enantioselectivity of the 1,3-dipolar cycloaddition reaction of C-phenyl-N-benzyl nitrone with 1,1-dimethoxypropene in the synthesis of **13** (Chapter 4)

Catalytic asymmetric 1,3-dipolar cycloadditions of the cyclic nitrone 3,4-dihydroisoquinoline N-oxide with ketene acetals affords a simple stategy for the preparation of homochiral 1-substituted isoquinolines These compounds constitue the largest class of alkaloid compounds known to date For example, the chiral oxazaborolidine catalyzed 1,3-dipolar cycloaddition of 3,4-dihydroisoquinoline N-oxide with 1,1-diethoxyethene afforded 5,5-diethoxyisoxazolidine **18** (R_1=H, R_2=Et), as described in Chapter 3

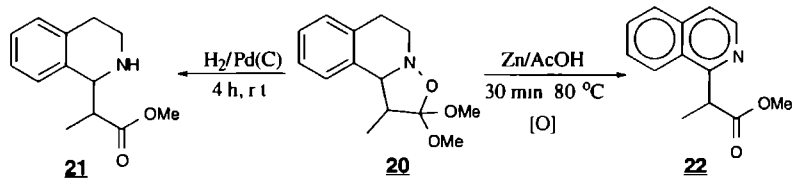
Scheme 8



The cycloadduct was converted by hydrogenolysis with H_2 on Pd/C (68 hrs, 40 psi bar H_2 in ethanol, c y >95%) into the known 1,2,3,4-tetrahydroisoquinoline ethyl ester **19**[22a] (*Scheme 8*) β-Amino ester **19** is the key intermediate for the synthesis of various biologically active compounds, such as diazasteroids[22a], 3-benzazocines (analgetica)[22b], 1,6,7,11b-tetrahydro-2H,4H-[1,3]oxazino-[4,3-a]isoquinoline[22c], 8- en 9-azasteroids[22d], and emetine-derivatives[22e]

The related 4-methyl-5,5-dimethoxyisoxazolidine **20**, prepared from the chiral oxazaborolidine catalyzed 1,3-dipolar cycloaddition of 3,4-dihydroisoquinoline N-oxide and 1,1-dimethoxypropene (Chapter 3) was analogously transformed into the corresponding β-amino methyl ester **21** via N-O bond cleavage with H_2 on Pd(C) at room temperature No reaction, i e N-O bond cleavage, occurred in the presence of H_2/Raney nickel at various (elevated) temperatures

Scheme 9



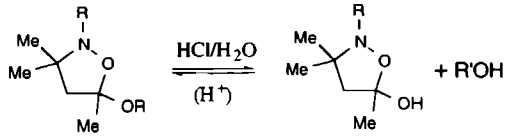
21 **20** **22**

Interestingly, the treatment of **20** with activated zinc dust in acetic acid at 80 °C under aerobic conditions gave isoquinoline ester **22** instead of the expected β–amino ester **21** (*Scheme 9*) Under argon atmosphere the reaction with zinc and acetic acid led selectively to the β–amino ester **21**[23]

6.2.2 Acidic Hydrolysis of 5,5-dialkoxyisoxazolidines

The behaviour of isoxazolidines toward acids depends strongly on the nature of the substituents[24] The ring of N-unsubstituted and N-alkyl- or N-aryl-substituted compounds is stable under mild conditions Under strong conditions, N-O cleavage may occur and open-chain compounds are formed, when hydroxy or alkoxy groups are present on the heterocyclic ring, elimination of water or alkanol can compete with or prevail over N-O cleavage, leading to isoxazolines Several reactions are known which modify the side chains without affecting the heterocyclic ring of isoxazolidines For example, 5-alkoxyisoxazolidines **23** are easily hydrolyzed by acid, as expected from their acetal-type structure, to give the 5-hydroxyisoxazolidine **24** under elimination of methanol or ethanol Conversely, the alkoxy compound is easily reformed by alkylation of the hemiacetal with methanol or ethanol catalyzed by traces of acid (*Scheme 10*)[25]

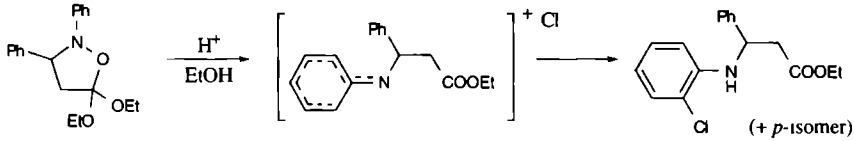
Scheme 10



23 **24**

Similarly, treatment of 5,5-dialkoxyisoxazolidines with acid is expected to yield the corresponding isoxazolidinones[26] via the formation of a hemi-orthoester analog Isoxazolidinones can be regarded as versatile intermediates for the preparation of β-amino acids via cleavage of the N-O bond by hydrogenolysis[26b] However, it was reported by Scarpati *et al* [16a] that treatment of 2,3-diphenyl-5,5-diethoxyisoxazolidine **10** with concentrated HCl in dioxane at 80 °C gives a mixture of ethyl 3-(*o*- and *p*-chloroanilino)-3-phenylpropionates **26**, probably due to the presence of an intermediate delocalized cation **25** (*Scheme 11*)

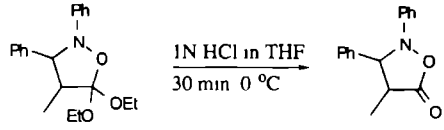
Scheme 11[16a]



10 **25** **26**

Some preliminary experiments were carried out to hydrolyze 5,5-dialkoxyisoxazolidines selectively to the corresponding isoxazolidinones under milder acidic conditions To this end 2,3-diphenyl-4-methyl-5,5-diethoxyisoxazolidine **8b** was treated with 1N HCl in THF for 30 minutes at 0 °C (*Scheme 12*)

Scheme 12



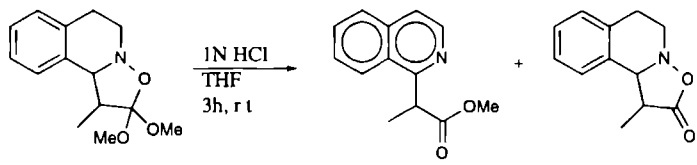
8b **27**

The product mixture was analyzed by GC/MS methods A mixture (*ca* 1 1) of the isoxazolidinone **27** and probably the corresponding β-hydroxyamino ester was obtained, although the mass peak of the latter was not found The mass of the fragmented N-hydroxy compound, i e the corresponding ion peak which closely resembles β amino ester **9b** was detected IR spectroscopy of the mixture showed an absorption at 1780 cm ^{1} which is characteristic for isoxazolidinone carbonyl functions[26] The formation of a N-hydroxy β-amino ester is not unlikely as such a reaction is similar to the formation of β-hydroxy esters by the acidic hydrolysis of 4,4-dialkoxyoxetanes[27] Subsequent elimination of the OH in the N-hydroxy compound under the acidic conditions will afford an imine, which was not detected Also no traces of aromatic substitution products, such as **26**, were observed Because of the disappointingly low chemoselectivity of the hydrolysis the reaction mixture was not further investigated No further attempts were undertaken to optimize the reaction conditions

The treatment of 1,2,3,4-tetrahydroisoquinoline isoxazolidine **20** with 1N HCl in THF at room temperature gave a 1 1 mixture (analyzed by GC) of the oxidized isoquinoline ester **22** and the isoxazolidinone **28** (m p 127 °C) (*Scheme 13*) Compound **20** could not be converted to the

isoxazolidinone **28** with complete selectivity by varying the reaction conditions For example, treatment of **20** with 1N HCl in toluene (4 hours at room temperature) or with a catalytic amount of *p*-toluenesulphonic acid (PTS) in methanol gave in both cases equimolar mixtures (analyzed by GC) of the isoxazolidinone **28** and the β-amino ester **22**

Scheme 13



20 **22** **28**

6.3 Conclusions

From the results described in this chapter the following conclusions can be drawn

1) Chiral 5,5-dialkoxyisoxazolidines, prepared by chiral oxazaborolidine catalyzed asymmetric 1,3-dipolar cycloaddition of nitrones with ketene acetals, can be transformed in one step to β-amino esters by hydrogenolysis of the N-O bond mediated by palladium catalysts
2) N-benzyl nitrones are particularly useful since tandem deprotection of the N-benzyl group in the corresponding isoxazolidine yields β-amino esters with a free amino group
3) Nitrones, ketene acetals and chiral oxazaborolidines can be prepared on a large scale from inexpensive starting material, such as aldehydes, hydroxylamines, alcohols and α-amino acids Although the enantiocontrol of the cycloaddition step need further improvement the 1,3-dipolar cycloaddition of nitrones with ketene acetals followed by hydrogenolysis provides a cheap, simple and truly catalytic two-step route for the asymmetric synthesis of β-amino esters
4) The acidic hydrolysis of chiral 5,5-dialkoxyisoxazolidines for the preparation of isoxazolidin-5-ones, which are versatile intermediates for chiral β-amino acids, is as yet not selective enough A more efficient procedure is required

6.4 Experimental Section

Dichloromethane was dried and distilled on CaH_2 ^{1}H-NMR spectra and ^{13}C-NMR were recorded on a Varian EM 390 (90 MHz, CW), a Bruker AM-100 (100 MHz, FT) or a Bruker AM-400 (400 MHz, FT) spectrometer with TMS as internal standard Decoupling experiments were run with DEPT 135 IR spectra were run on a Perkin-Elmer 298 spectrophotometer Mass spectra were measured with a Varian SM1-B double focussing mass spectrometer or with a VG 7070E mass spectrometer Gas chromatography was performed on a Hewlett-Packard 5710A GC-instrument equipped with a capillary HP cross-linked methyl silicone column (type PAS 017, 25 m x 0 31 mm)

Purification was done by "flash"-chromatography with Merck silicagel 60H as the stationary phase

syn-Methyl-3-anilino-2-methyl-3-phenylpropionate 9a[18]

The *cis*-isoxazolidine **8a** (200 mg, 0 67 mmol) was dissolved in 15 ml ethanol, 10% Pd(C) (ca 100 mg) was added and the mixture was hydrogenated at room temperature under 1atm H_2-pressure for 30-60 minutes under stirring The reaction mixture was filtered over a small amount of Celite, washed 2 times with 10 ml ethanol and concentrated under vacuum to yield the solid *syn*-β-amino ester **9a** (174 mg, 96% yield) m p 98 °C (lit 98-99 °C[18]), 400 MHz ^{1}H NMR δ(ppm) 1 55 3H, d, J = 7 1 Hz, 2-CH_3, 2 96 1H, quintet, J = 7 1 Hz and J = 5 0 Hz, H-2, 3 61 3H, s, OCH_3, 4 49 1H, broad s, NH (D_2O exchange), 4 72 1H, d, J = 5 0 Hz, H-3, 6 51 2H, d, J = 8 1 Hz, 2x ortho-N-ArH, 6 64 1H, t, J = 7 3 Hz, para-N-ArH, 7 07 2H, t, J = 7 3 and 8 1 Hz, 2x meta N-ArH, 7 22 7 31 5H, m, ArH Doublet signal at 1 55 ppm (2-Me) and doublet at 4 72 ppm (H-3) become singlets after irradiation of H-2 resonance at 2 96 ppm ^{13}C NMR δ(ppm) 11 8 (2-CH_3), 46 0 (C-2), 51 9 (O$\underline{C}H_3$), 59 6 (C-3), 113 6 (2x C_{ortho} N-Ar), 117 6 (C_{para} N-Ar), 126 8 (2x C_{meta} N-Ar), 127 3, 128 5, 129 0, 140 6 (2x C_{ipso}), 174 6 (C=O) Enantioselectivity was determined by HPLC on CHIRALCEL OD, UV detection at 226 nm, flow rate 1 0 ml/min , eluens *n*-hexane/2-PrOH = 95/5 (v/v), 6 69 min (major product) and 7 46 min (minor)

syn-Ethyl-3-anilino-2-methyl-3-phenylpropionate 9b[18]

Hydrogenolysis of isoxazolidine **8b** to β-amino ester **9b** was performed according to the procedure described for **9a** Oil, IR (cm $^{-1}$) 1720 (C=O), 400 MHz ^{1}H NMR δ(ppm) 1 14 3H, t, J = 7 1 Hz, CH_3-CH_2, 1 15 3H, d, J = 7 1 Hz, 2-CH_3, 2 94 1H, quintet, J = 7 1 Hz and J = 5 2 Hz, H-2, 4 06 2H, q, J = 7 1 Hz, OCH_2CH_3, 4 49 1H, broad s, NH (D_2O exchange), 4 71 1H, d, J = 5 2 Hz, H-3, 6 51 2H, d, J = 8 1 Hz, 2x ortho-N-ArH, 6 64 1H, t, J = 7 3 Hz, para-N-ArH, 7 07 2H, t, J = 7 3 and 8 1 Hz, 2x meta N-ArH, 7 22-7 31 5H, m, ArH ^{13}C NMR δ(ppm) 11 9 (2-CH_3), 14 1 (CH_3), 46 2 (C-2), 59 7 (C-3), 60 7 (O$\underline{C}H_2$), 113 6 (2x C_{ortho} N-Ar), 117 6 (C_{para} N-Ar), 126 9 (2x C_{meta} N-Ar), 127 3, 128 5, 129 0, 140 6 (C_{ipso}), 147 0 (C_{ipso}), 174 2 (C=O) GC-MS HRMS (rel int) $C_{18}H_{21}NO_2$ 284 (M^++1, 4), 283 (M^+, 4), 183 (14), 182 (100), 167 (1), 135 (1), 117 (7), 104 (21)

syn-*n*-Propyl-3-anilino-2-methyl-3-phenylpropionate 9c

Hydrogenolysis of isoxazolidine **8c** to β-amino ester **9c** was performed as described for **9a** IR (cm $^{-1}$) 1720 (C=O), 400 MHz ^{1}H NMR δ(ppm) 0 83 3H, t, J = 7 4 Hz, CH_2CH_3, 1 16 2H, d, J = 7 2 Hz, 2-CH_3, 1 55 2H, m, J = 7 1 and 7 4 Hz, $CH_2CH_2CH_3$, 2 95 1H, quintet, J = 7 2 Hz and J = 5 2 Hz, H-2, 3 97 2H, dt, J = 7 1 Hz, $OCH_2CH_2CH_3$, 4 49 1H, broad s, NH (D_2O exchange), 4 71 1H, d, J = 5 2 Hz, H-3, 6 51 2H, d, J = 8 1 Hz, 2x ortho-N-ArH, 6 64 1H, t, J = 7 3 Hz, para-N-ArH, 7 06 2H, t, J = 7 3 and 8 1 Hz, 2x meta N-ArH, 7 22-7 31 5H, m, ArH ^{13}C NMR δ(ppm) 10 3 (2-CH_3), 12 0 (CH_3), 21 8 ($CH_2\underline{C}H_2CH_3$), 46 2 (C-2), 59 7 (C-3), 66 4 (O$\underline{C}H_2$), 113 6 (2x C_{ortho} N-Ar), 117 5 (C_{para} N-Ar), 126 9 (2x C_{meta} N-Ar), 127 3, 128 4, 129 0, 140 7 (C_{ipso}), 147 0 (C_{ipso}), 174 2 (C=O) GC-MS HRMS (rel int) $C_{19}H_{23}NO_2$ 299 (M^++1, 17), 298 (M^+, 100), 183 (12), 182 (50), 149 (7), 117 (7), 104 (20)

syn-Isopropyl-3-anilino-2-methyl-3-phenylpropionate 9d

Hydrogenolysis of isoxazolidine **8d** to β-amino ester **9d** was performed as described for **9a** A mixture of *ca* 85/15 syn/anti product was isolated and analyzed IR (cm $^{-1}$) 1720 (C=O), 400 MHz ^{1}H NMR δ(ppm) 1 05 3H, d, J = 6 2 Hz, OCH(CH$_3$)C*H$_3$*, 1 14 3H, d, J = 7 1 Hz, 2-CH$_3$, 1 17 3H, d, J = 6 2 Hz, OCH(C*H$_3$*)CH$_3$, 2 88 1H, quintet, J = 5 5 Hz and J = 7 1 Hz, H-2, 4 21 1H, broad s, NH, 4 60 1H, d, J = 5 5 Hz, H-3, 4 93 1H, dq, J = 6 3 Hz, OC*H*(CH$_3$)$_2$, 6 46 2H, m, 2x ortho-N-ArH, 6 65 2H, m, 2x meta N-ArH, 7 20-7 32 6H, m, ArH ^{13}C NMR δ(ppm) 10 3 (2-CH$_3$), 12 0 (CH$_3$), 21 8 (CH$_2$CH$_2$CH$_3$), 46 2 (C-2), 59 7 (C-3), 66 4 (OCH$_2$), 113 6 (2x C$_{ortho}$ N Ar), 117 5 (C$_{para}$ N-Ar), 126 9 (2x C$_{meta}$ N-Ar), 127 3, 128 4, 129 0, 140 7 (C$_{ipso}$), 147 0 (C$_{ipso}$), 174 2 (C=O) In the NMR-spectrum of the mixture some characteristic resonances were visible which we ascribe to the *anti isopropyl 3-anilino-2-methyl-3-phenyl-propionate* 400 MHz ^{1}H NMR δ(ppm) 2 76 1H, quintet, *anti* H-2, 4 40 1H, d, J = 7 Hz, *anti* H-3, all other resonance signals overlapped with syn product

Ethyl-3-anilino-3-phenylpropionate 11[18]

To a solution of the crude isoxazolidine **10** (313 mg, 1 mmol) in methanol-water-acetic acid (20 2 1, 10 ml) was added Pd(OH)$_2$-C (Pearlman's catalyst, 250 mg) and the resultant black suspension was stirred under a hydrogen balloon for 5 hrs The reaction mixture was filtered through a plug of Celite, washed with methanol and the filtrate was concentrated to give a white residue This residue was dissolved in saturated aqueous NaHCO$_3$ and the solution was subsequently extracted with dichloromethane The combined organic extracts were dried (MgSO$_4$), filtered and evaporated to afford the β-amino ester **11** (80% yield) as an oil, IR (cm $^{-1}$) 1715 (C=O), 400 MHz ^{1}H NMR δ(ppm) 1 27 3H, t, J = 7 1 Hz, C*H$_3$*-CH$_2$, 2 51 1H, dd, J = 6 0 and 15 2 Hz, CH*H*C=O, 2 61 1H, dd, J = 6 0 and 15 2 Hz, C*H*HC=O, 3 80 1H, broad s, NH, 3 96 1H, m, H-3, 4 16 2H, q, J = 7 1 Hz, OC*H$_2$*CH$_3$, 6 51 2H, m, 2x ortho-N-ArH, 6 64 1H, m, para-N ArH, 7 10-7 47 7H, m, ArH ^{13}C NMR δ(ppm) 19 4 (CH$_3$), 39 4 (C-2), 50 2 (C 3), 60 4 (OCH$_2$), 113 4 (2x C$_{ortho}$ N Ar), 117 4 (C$_{para}$ N-Ar), 126 3 (2x C$_{meta}$ N-Ar), 128 7, 129 1, 142 2 (C$_{ipso}$), 147 3 (C$_{ipso}$), 172 0 (C=O) GC-MS HRMS (rel int) C$_{17}$H$_{19}$NO$_2$ 269 (M$^+$, 30), 182 (100), 104 (26)

Methyl (*2R,3R*)-3-amino-2-methyl-3-phenylpropionate 13[12g h]

To a solution of the crude isoxazolidine **12** (299 mg, 1 mmol) in methanol-water-acetic acid (20 2 1, 10 ml) was added Pd(OH)$_2$ on carbon (Pearlman s catalyst, 250 mg) and the resultant black suspension was stirred under a hydrogen balloon for 5 hrs The reaction mixture was filtered through a plug of Celite, washed with methanol and the filtrate was concentrated to give a white residue This residue was dissolved in saturated aqueous NaHCO$_3$ and the sp,ution was subsequently extracted with dichloromethane The combined organic extracts were dried (MgSO$_4$), filtered and evaporated to afford the free amino ester (2R,3R)-**13** (175 mg, 90% yield) The absolute configuration was derived from the fact that the product had a negative optical rotation The enantiomer (2S,3S)-**13** has positive rotation [α]$_D^{25}$ = +15 8 (c 1 00, CHCl$_3$)[12h] 400 MHz ^{1}H NMR δ (ppm) 1 16 3H, d, J = 7 1 Hz, 2-CH$_3$, 1 68 2H, br s, NH$_2$, 2 76 1H, dq, J = 5 9 and 7 1 Hz, H-2, 3 58 3H, s, OCH$_3$,

4 29 1H, d, J = 5 9 Hz, H-3, 7 24 1H, m, *para*-ArH, 7 26-7 32 4H, m, ArH ^{13}C NMR δ(ppm) 11 9 (2 CH_3), 47 2 (C-2), 51 5 (OCH_3), 57 3 (C-3), 126 5, 127 2, 128 3 (Ar-C), 143 6 (C_{ipso}), 175 4 (C=O) HRMS (rel int) m/e 193 (M^+, 0 3), 178 (-CH_3, 7), 177 (55), 158 (2), 145 (3), 132 (4), 122 (8), 121 (100), 105 (10) Peak Match $C_{11}H_{15}NO_2$ M_{calc} = 193 1103, M_{found} = 193 11021 ± 0 00097 The enantioselectivity of the reaction was determined by HPLC using a chiral Daicel HPLC column type CHIRALCEL OD, UV detection at 226 nm, eluent *n*-hexane/2-PrOH = 99/1 (v/v), flow rate 1 0 ml/min , (*2R,3R*)-**13** 22 2 min , (*2S,3S*)-**13** 36 0 min **The** enantioselectivity was also determined by NMR-analysis of the derivatized Mosher-amides The β-amino ester (*2S,3S*)-**13** (HPLC 57% ee) was dissolved in dichloromethane and the (*R*)-Mosher acid chloride was added After stirring at room temperature for 2 hrs the crude mixture was separated by flash chromatography on silica gel to afford the pure Mosher amides as a mixture of two diastereomers oil, 400 MHz ^1H NMR δ (ppm) 1 11 0 64H, d, J = 7 1 Hz, 2-CH_3 (2R,3R), 1 17 2 36H, d, J = 7 1 Hz, 2-CH_3 (2S,3S), 3 02 1H, m, H-2, 3 38 0 64H, s, OMe, 3 47 2 36H, s, OMe (2S 3S) 3 56 0 64H, s, OMe, 3 60 2 36H, s, OMe (2S,3S), 5 32 1H, m, H-3, 7 13 1H, m, NH, 7 23 7 43 10H, m, ArH ^{13}C NMR δ (ppm) 12 8 (2-Me, (2R,3R)), 13 1 (2-Me, (2S,3S)), 44 4 (C-2, (2R,3R), 44 5 (C-2, (2S,3S)), 51 9 (OMe), 55 0 and 55 1 (OMe), 77 2, 122 3, 125 1, 126 7, 126 9, 127 5, 127 6, 127 8, 128 4, 128 5, 129 4, 129 8, 132 4, 138 6 (Ar-C), 165 5 (C=O), 173 9 (C=O) ^{19}F NMR δ (ppm) 11 00 s, CF_3 and 11 04 s, CF_3 (2S,3S) The resolution was not good enough to give reliable integration HRMS (rel int) m/e 410 (M^{+1}, 0 3), 378 (-OMe, 2), 322 (10), 220 (20), 189 (32), 177 (55), 145 (3), 132 (3), 121 (100) Peak Match $C_{21}H_{22}NO_4F_3$ M_{calc} = 409 1500, M_{found} = 409 1501 ± 0 001

Methyl *syn*-2-amino-3-methyl-pentanoate 17[4 12m]

The chiral oxazaborolidines **15** were prepared *in situ* at room temperature under a dry nitrogen atmosphere from the N tosyl α–amino acids by addition of equimolar amounts of BH_3-THF (1M in THF) or BH_3-SMe_2 (1M in toluene) in 5 ml solvent The 1,3-dipolar cycloaddition of C-ethyl-N-benzyl nitrone **14**[20] with 1,1-dimethoxypropene was performed at -78 °C in the presence of 20 mol% of chiral oxazaborolidines **15** The nitrone (3 5 mmol) was added at room temperature, the mixture was cooled to -78 °C and the ketene acetal (3 equiv) was added After 5 hrs the reaction mixture was quenched with saturated aqueous bicarbonate, extracted with dichloromethane, dried (Na_2SO_4) and concentrated under vacuum to give an oily residue The crude cycloadduct N-benzyl-5,5-dimethoxyisoxazolidine **16** was not isolated but immediately converted to the β-amino ester **17** via hydrogenolysis with H_2 (1 atm) and $Pd(OH)_2/C$ as the catalyst, according to the procedure described for the preparation of β-amino ester **13** Purification by flash chromatography using ether methanol (1 30, v/v) as eluent gave the β-amino ester **17** (yield 77%) Oil, IR (cm ^{1}) 1735 (C=O), 100 MHz ^1H-NMR (in $CDCl_3$) δ (ppm) 0 89 3H, t, J = 6 9 Hz, CH_3CH_2, 1 07 3H, d, J = 7 0 Hz, 2 CH_3 1 24 2H, m, CH_2CH_3, 1 65 2H, br s, NH_2, 2 44 1H, m, H 2, 2 90 1H, m, H-3, 3 63 3H s OCH_3 The enantiomeric excess of **17** was determined by HPLC using a Daicel Chiralcel OD column, UV detection at 226 nm eluent *n* hexane/2-PrOH 99/1 (v/v), flow rate 1 0 ml/min , 13 60 min (major isomer) and 13 74 min (minor isomer) GC analysis of the corresponding

diastereomeric Mosher-amides gave similar results

Ethyl (1,2,3,4-tetrahydro-1-isoquinolyl) acetate 19[22a]

All physical data of this compound agreed well with literature data[22] Oil, IR (cm ^{1}) 1735 (C=O), 100 MHz ^{1}H-NMR (in $CDCl_3$) δ (ppm) 1 25 3H, t, J = 7 Hz, CH_2CH_3, 2 27 1H, br s, NH, 2 7-3 5 6H, m, 4 17 2H, q, J = 7 Hz, CH_2CH_3, 4 45 1H, m, 7 1 4H, m, ArH

2-(1,2,3,4-Tetrahydro-isoquinolin-1-yl)-propionic acid methyl ester 21

The isoxazolidine **20** (200 mg, 0 80 mmol) was hydrogenated with H_2/Pd(C) (40 psi bar) in 15 ml ethanol After 68 hrs the mixture was filtered over Hyflo and concentrated under vacuum to yield β-amino ester **21** (167 mg, 0 76 mmol, 95% yield) as an oil IR (cm^{-1}) 1728 (C=O), 400 MHz ^{1}H NMR δ (ppm) 1 29 3H, d, $J_{4CH3,H4}$ =7 13 Hz, 4-CH_3, 1 5-2 5 1H, N-H, 2 74 2H, m, H-8, 2 95 1H, ddd, H-9, 3 09 1H, dq, H-4, 3 27 1H, ddd, H-9', 3.60 3H, s, 5-OCH_3, 4 14 1H, d, $J_{H3,H4}$ = 6 4 Hz, H-3, 7 11 4H, m, H-7, H-8, H-9 en H-10 ^{13}C NMR δ (ppm) 15 1 (4-CH_3), 29 4 (C-12), 40 9 (C-13), 44 3 (C-4), 51 5 (5-OCH_3), 58 3 (C-3), 125 4 (C-7), 126 3 (C-10), 126 6 (C-8), 129 3 (C-9), 135 7 (C-11), 136 9 (C-6), 175 8 (C-5) HRMS (rel int) = 219 (M^+, 0 4), 218 (1 4), 183 (1 1), 160 (2 3), 133 (13 8), 132 (100 0), Peak Match M_{calc}=219 1259, M_{fnd}=219 1259±0 00088

2-Isoquinolin-1-yl propionic acid methyl ester 22

Activated zinc dust was added in three portions to a stirred solution of isoxazolidine **20** (220 mg, 0 89 mmol) in 50 ml glacial acetic acid The reaction mixture was stirred at 80 °C for 30 min and subsequently neutralized with $NaHCO_3$ until evolution of CO_2 ceased After extraction with ethyl acetate and washing with water, the organic extracts were concentrated under vacuum and the residue purified by flash chromatography (eluent ethylacetate/hexane 4 3, v/v) to give the isoquinoline ester **22** (173 mg, 0 80 mmol, 90% yield) as an oil IR (cm^{-1}) 2250 (C=N), 1725 (C=O), 400 MHz ^{1}H-NMR δ (ppm) 1 70 3H, d, J = 7 1 Hz, 9-CH_3; 3 69 3H, s, OCH_3, 4 74 1H, q, J = 7 1 Hz, H-9, 7 57 1H, d, J = 5 6 Hz, H-4, 7 63 1H, dd, $J_{H6,H5}$ = 8 1 Hz, $J_{H6,H7}$ = 7 3 Hz, H-6, 7 69 1H, dd, $J_{H7,H6}$ = 7 3 Hz,$J_{H7,H8}$ = 8 4 Hz, H-7, 7 85 1H, d, J = 8 1 Hz, H-5, 8 15 1H, d, J = 8 4 Hz, H-8, 8 49 1H, d, J = 5 6 Hz, H-3 ^{13}C-NMR δ (ppm) 16 8 (9-CH_3), 44 3 (C-9), 52 2 (OCH_3), 120 1 (C-4), 124 5 (C-8), 126 4 (C-8a), 127 5 (C-5), 127 6 (C-7), 129 9 (C-6), 136 5 (C-4a), 142 0 (C-3), 159 5 (C-1), 174 0 (C=O) HRMS (rel int , m/e) 215 (M^+, 48), 200 (18), 184 (9), 156 (100), 128 (35), 115 (3) Peak Match Calcd 215 0946 Found 215 0946

Hydrolysis of isoxazolidine 8b with diluted acid

Diluted hydrochloric acid (5 ml 1N HCl) was added dropwise to a solution of isoxazolidine **8b** (1 mmol) in 15 ml THF at 0 °C After stirring the reaction mixture for 30 min , 30 ml of diethyl ether was added and the whole mixture was washed twice with saturated aqueous $NaHCO_3$ (15 ml) The organic layer was dried (Na_2SO_4) and concentrated under vacuum The residue was analyzed by GC It contained a *ca* 1 1 mixture of the β-amino ester **9b** (proved by addition of pure **9b** to the

mixture which caused enhancement of the GC-signals of this compound) and probably the isoxazolidinone **27** (IR absorption at 1780 cm^{-1}) Because of the disappointingly low chemoselectivity of the reaction the residue was not further purified

1-Methyl-1,4,5,9b-tetrahydro-3-oxa-3a-aza-cyclopenta[a]naphtalen-2-one 28

Diluted hydrochloric acid (2 ml 1N HCl) was added dropwise to a solution of isoxazolidine **20** (0 71 mmol) in 2 ml THF After stirring the reaction mixture for 3 hrs at room temperature, 25 ml diethyl ether was added and the whole mixture was washed twice with saturated aqueous $NaHCO_3$ (10 ml) The organic layer was dried (Na_2SO_4) and concentrated under vacuum The residue contained a *ca* 1 1 mixture of the β-amino ester **21** and the isoxazolidinone **28** as analyzed by GC The residue was purified by flash chromatography (eluent ethylacetate/hexane 1 4, v/v) to give the isoxazolidinone **28** (37% yield) as a white solid (m p 127 °C) IR (cm ^{1}) 1780 (C=O), 400 MHz ^{1}H-NMR ($CDCl_3$) δ (ppm) 1 54 3H, d, J = 7 1 Hz, 1-CH_3, 2 91-3 00 2H, m, H-5, H-5', 3 07 1H, dq, J = 7 1 Hz, J = 9 5 Hz, H-1, 3 37 1H, m, H-4', 3 56 1H, m, H-4, 4 65 1H, d, J = 9 5 Hz, H-9b, 7 15 2H, m, H-7, H-8, 7 25 2H, m, H-6, H-9 ^{13}C-NMR δ (ppm) 14 0 (1-CH_3), 27 1 (C-5, CH_2), 41 7 (C-1), 50 2 (C-4, CH_2), 67 7 (C-9b), 126 7 (C-7), 126 9 (C-6), 127 7 (C-8), 128 7 (C 9), 132 6 (C 5a), 133 0 (C-9a), 179 0 (C-2, C=O) HRMS (rel int) 203 (M^+, 37), 158 (4), 147 (100), 130 (23), 115 (16)

6.5 References and Notes

1 Gueritte-Voegelein, F , Senilh, V , David, B , Guenard, D , Potier, P *Tetrahedron* **1986**, *42*, 4451 Mangatal, L , Adeline, M T , Guenard, D , Gueritte-Voegelein, F *Tetrahedron* **1989**, *45*, 4177, Ishizuka, M , Mastida, T , Kanbayashi, N , Fukasawa, S , Takeuchi, T , Aoyagi, T , Umezawa, H *J Antibiot* **1980**, *33*, 642, Okura, A , Ishizuka, M , Takeuchi, T *J Antibiot* **1988**, *41*, 261

2 a) For cyclization of β-amino acids to β-lactams see Mayachi, N , Shibasaki, M *J Org Chem* **1990**, *55*, 1975, Kim, S , Lee, P H , Lee, T A *J Chem Soc , Chem Commun* **1988**, 1242, Tanner, D , Somfai, P *Tetrahedron* **1988**, *44*, 613, Kunieda, T , Nagamatsu, T , Kiguchi, T , Hirobe, M *Tetrahedron Lett* **1988**, *29*, 2203, Huang, H , Iwasawa, N , Mukaiyama, T *Chem Lett* **1984**, 1465 b) For other methods see Vorbruggen, H , Woodward, R B *Tetrahedron* **1993**, *49*, 1625, Wang, W -B , Roskamp, E J *J Am Chem Soc* **1993**, *115*, 9417, Guzzo, P R , Miller, M J *J Org Chem* **1994**, *59*, 4862, Veinberg, G A , Lukevics, E *Heterocycles* **1994**, *38*, 2309, c) For recent reviews on the synthesis of β-lactams see *The Organic Chemistry of β-lactams* Georg, G I , Ed , VCH, **1993**, Van der Steen, F H , Van Koten, G *Tetrahedron* **1991**, *47*, 7503, Hart, D J , Ha, D C *Chem Rev* **1989**, *89*, 1447, Backes, J , *2-Oxo-azetidine (β-Lactame)* in Houben-Weyl, Methoden der Organischen Chemie, Georg Thieme, Stuttgart, **1991**, Band E16b, pp 31-868

3 For reviews on stereoselective synthetic approaches to β-amino acids see Cole, D C

Tetrahedron **1994**, *50*, 9517, Juaristi, E , Quintana, D , Escalante, J *Aldrichimica Acta* **1994**, *27*, 3 and references cited therein

4 For recent asymmetric syntheses of (2*S*,3*R*)-2-methyl-3-aminopentanoic acid see a) Bates, R B , Gangwar, S *Tetrahedron Asymmetry* **1993**, *4*, 69, b) Davies, S G , Ichihara, O , Walters, I A S *Synlett* **1994**, 117, c) Jefford, C W , McNulty, J *Helv Chim Acta* **1994**, *77*, 2142

5 a) Carter, D C , Moore, R E , Mynderse, J S , Niemczure, W P , Todd, J S *J Org Chem* **1984**, *49*, 236, b) Mynderse,J S , Hunt, A H , Moore, R E *J Nat Prod* **1988**, *51*, 1299, c) Petit, G R , Kamano, Y , Kizu, H , Dufresne, C , Herald, C L , Botems, R J , Schmidt, J M , Boettner, F E , Nieman, R A *Heterocycles* **1989**, *28*, 553

6 a) Okino, T , Matsuda, H , Murakami, M , Yamaguchi, K *Tetrahedron Lett* **1993**, *34*, 501, b) Bunnage, M E , Burke, A J , Davies, S G *Tetrahedron Asymmetry* **1994**, *5*, 203, c) Matsuura, F , Hamada, Y , Shioiri, T *Tetrahedron* **1994**, *50*, 11303

7 Palomo, C , Aizpura, J M , Cuevas, C *J Chem Soc , Chem Commun* **1994**, 1957

8 a) Hattori, K , Yamamoto, H *Tetrahedron* **1994**, *50*, 2785, b) Sasai, H , Kim, W S , Suzuki, T , Shibasaki, M *Tetrahedron Lett* **1994**, *35*, 6123, c) Iizuka, K , Kamijo, T , Harada, H , Akahane, K , Kubota, T , Umeyama, H , Kiso, Y *J Chem Soc Chem Commun* **1989**, 1687

9 a) Wang, Z -M , Kolb, H C , Sharpless, K B *J Org Chem* **1994**, *59*, 5104, b) Kanazawa, A M , Denis, J -N , Greene, A E *J Org Chem* **1994**, *59*, 1238 and references cited therein, c) Koskinen, A M P , Karvinen, E K , Siirila, J P *J Chem Soc , Chem Commun* **1994**, 21, d) Srivastava, R P , Zjawiony, J K , Peterson, J R , McChesney, J D *Tetrahedron Lett* **1994**, *5*, 1683, e) Bunnage, M E , Davies, S G , Goodwin, C J *J Chem Soc Perkin Trans I* **1994**, 2385, f) Palomo, C , Aizpura, J M , Miranda, J I , Mielgo, A , Odriozola, J M *Tetrahedron Lett* **1993**, *34*, 6325, g) Bourzat, J D , Commercon, A *Tetrahedron Lett* **1993**, *34*, 6049, h) Swindell, C S , Tao, M *J Org Chem* **1993**, *58*, 5889, i) Davis, F A , Reddy, R T , Reddy, R E *J Org Chem* **1992**, *57*, 6387

10 Alcon, M , Canas, M , Poch, M , Moyano, A , Pericas, M A , Riera, A *Tetrahedron Lett* **1994**, *35*, 1589, Cimarelli, C , Palmieri, G , Bartoli, G *Tetrahedron Asymmetry* **1994**, *5*, 1455,

11 a) For BINAP-Ru(II) catalyzed hydrogenation of β-substituted acrylic acids see Lubell, W D , Kitamura, M , Noyori, R *Tetrahedron Asymmetry* **1991**, *2*, 543, b) For the first example of enantioselective synthesis of chiral β-amino acid esters from achiral imines using a chiral boron complex see Corey, E J , Decicco, C P , Newbold, R C *Tetrahedron Lett* **1991**, *32*, 5287

12 a) Davies, S G , Ichihara, O *Tetrahedron Asymmetry* **1991**, *2*, 183, b) Davies, S G , Garrido, N M , Ichihara, O , Walters, I A S *J Chem Soc Chem Commun* **1993**, 1153, c) Davies, S G , Ichihara, O , Walters, I A S *Synlett*, **1993**, 461, d) Bunnage, M E , Davies, S G , Goodwin, C J *J Chem Soc , Perkin Trans I*, **1993**, 1375, e) Bunnage, M E , Davies, S G , Goodwin, C J *Synlett*, **1993**, 731, f) Davies, S G , Walters, I A S *J Chem Soc Perkin Trans I* **1994**, 1129, g) Davies, S G , Ichihara, O , Walters, I A S *J Chem Soc*

Perkin Trans I **1994**, 1141, h) Davies, S G , Garrido, N M , Ichihara, O , Walters, I A S *J Chem Soc Perkin Trans I* **1994**, 1153, i) Bunnage, M E , Davies, S G , Goodwin, C J *J Chem Soc Perkin Trans I* **1994**, 1375, j) Davies, S G , Ichihara, O , Lenoir, I , Walters, I A S *J Chem Soc Perkin Trans I* **1994**, 1411, k) Bunnage, M E , Davies, S G , Goodwin, C J *J Chem Soc Perkin Trans I* **1994**, 2373, l) Bunnage, M E , Davies, S G , Goodwin, C J *J Chem Soc Perkin Trans I* **1994**, 2385, m) Davies, S G , Ichihara, O , Walters, I A S *Synlett* **1994**, 117, n) Bunnage, M E , Burke, A J , Davies, S G , Goodwin, C J *Tetrahedron Asymmetry* **1994**, *5*, 203, o) Costello, J F , Davies, S G , Ichihara, O *Tetrahedron Asymmetry* **1994**, *5*, 1999

13 For related asymmetric Michael additions of metal amides to α,β-unsaturated esters see a) chiral lithium amide addition to dienoate Asao, N , Tsukada, N , Yamamoto, Y *J Chem Soc Chem Commun* **1993**, 1660, b) chiral magnesium amide addition Bunnage, M E , Davies, S G , Goodwin, C J , Walters, I A S *Tetrahedron Asymmetry* **1994**, *5*, 35, c) chiral lithium salt Hawkins, J M , Lewis, T A *J Org Chem* **1992**, *57*, 2114, Hawkins, J M , Lewis, T A *J Org Chem* **1994**, *59*, 649, d) titanium dialkylamide Hosomi, A , Yanagi, T , Hojo, M *Tetrahedron Lett* **1991**, *32*, 2371, e) dimethylaluminium amide Basha, A , Lipton, M , Weinreb, S M *Tetrahedron Lett* **1977**, *18*, 4171, f) lithiated TMS SAMP Enders, D , Bettray, W , Raabe, G , Runsink, J *Synthesis*, **1994**, 1322, Enders, D , g) Wahl, H , Bettray, W *Angew Chem* **1995**, *107*, 527

14 a) Hattori, K , Miyata, M , Yamamoto, H *J Am Chem Soc* **1993**, *115*, 1151, b) Hattori, K , Yamamoto, H *Synlett* **1993**, 239, c) Hattori, K , Yamamoto, H *BioMed Chem Lett* **1993**, *3*, 2337, d) Ishihara, K , Kuroki, Y , Yamamoto, H *Synlett* **1995**, 41, see also ref 8a

15 a) Tufariello, J J In *1,3-Dipolar Cycloadditions Chemistry*, Padwa, A , Ed , Wiley, New York, **1984**, vol 2, pp 83-168, b) Confalone, P N , Huie, E M *Org React* **1988**, *36*, 1-173, c) Balasubramanian, N *Org Prep Proc Int* **1985**, 25, d) Black, D S , Crozier, R F , Davis, V C *Synthesis*, **1975**, 205-221, e) Annunziata, R , Cinquini, M , Cozzi, F , Raimondi, L *Gazz Chim Ital* **1989**, *119*, 253-269, f) Mulzer, J *Nachr Chem Tech Lab* **1984**, *32*, 882-887, g) Torssell, K B G *Nitrile Oxides, Nitrones, and Nitronates in Organic Synthesis*, VCH Weinheim, **1988**, pp 1-47, 75-89, 129-327, h) Dopp, D , Dopp, H in Houben-Weyl- Methoden der Organischen Chemie", vol E14b, Klamann, D , Hagemann, H , Eds , Georg Thieme Verlag Stuttgart, **1990**, i) Grunanger, P , Vita-Finzi, P "The Chemistry of Heterocyclic Compounds , Taylor, E C , Ed , Vol 49, Part 1, John Wiley & Sons, New York, **1991**, Chapter 3 Isoxazolidines", pp 649-777

16 a) Scarpati, R , Sica, D , Santacroce, C *Gazz Chim Ital* **1966**, *96*, 375-386, b) Huisgen,R , Grashey, R , Seidl, H , Hauck, H *Chem Ber* **1968**, *101*, 2559-2563, c) Keirs, D , Moffat, D , Overton, K , Tomanek, R *J Chem Soc Perkin Trans I* **1991**, 1041-1051, d) Seerden, J -P G , Scholte op Reimer, A W A , Scheeren, J W *Tetrahedron Lett* **1994**, *35*, 4419-4422, e) Chapters 3 and 4 of this thesis

17 Grunanger, P , Vita-Finzi, P "The Chemistry of Heterocyclic Compounds", Taylor, E C , Ed , Vol 49, Part 1, John Wiley & Sons, New York, **1991**, Chapter 3 "Isoxazolidines", pp

649-777

18 a) Barluenga, J , Fananas, F J , Yus, M *J Org Chem* **1979**, *44*, 4798, b) Bartoli, G , Cimarelli, C , Marcantoni, E , Palmieri, G , Petrini, M *J Org Chem* **1994**, *59*, 5328

19 For general procedures for the synthesis of N-benzyl nitrones see a) Dondoni, A , Franco, S , Junquera, F , Merchán, F , Merino, P , Tejero, T *Synth Commun* **1994**, *24*, 2537-2550, b) Goti, A , De Sarlo, F , Romani, M *Tetrahedron Lett* **1994**, *35*, 6571-6574, c) Murahashi, S -I , Shiota, T , Imada, Y *Org Synth Vol 70*, **1992**, 265-271

20 Nitrone **11** was prepared from N-benzylhydroxylamine according to ref 19a

21 Dyke, S F , Kinsman, R G in "The Chemistry of Heterocyclic Compounds Isoquinolines , Grethe, G , Ed , Vol 38, Part 1, John Wiley & Sons, New York, **1981**, Chapter 1, pp 1 137, Popp, F D , Duarte, F F in "The Chemistry of Heterocyclic Compounds Isoquinolines , Kathawala, F G , Coppola, G M , Schuster, H F , Ed , Vol 38, Part 2, John Wiley & Sons, New York, **1990**, Chapter 2, pp 135-365

22 a) Koizumi, T , Yanagawa, Y , Yoshii, E , Yamazaki, T *Chem Pharm Bull* **1978**,*26*, 1308-1311, b) Pecherer, B , Stumpf, J , Brossi, A *Helv Chim Acta* **1970**, *53*, 763-770, c) Crabb, T A , Mitchell, J S , Newton, R F *J Chem Comm Perkin II*, **1977**, 370-378, d) Meyers, A I , Munoz, G G , Sobotka, W , Baburao, K *Tetrahedron Lett* **1965**, *4*, 255-260, e) Brossi, A , Lindlar, H , Walter, M , Schnider, O *Helv Chim Acta* **1958**, *41*, 119-139

23 Hermkens, P H H , Plate, R , Ottenheijm, H C J *Tetrahedron* **1988**, *44*, 1991

24 See ref 1i, pp 744-746

25 a) Belly, A , Jacquier, R , Petrus, F , Verducci, J *Bull Soc Chim Fr* **1972**, 3951, b) Rukasov, A F , Tashchi, V P , Kondratev, T A , Baskokov, Y A , Putsykin, Y G *Khim Geterotsikl Soedin* **1979**, 746, c) ref 1i, p 752

26 a) Stamm, H , Steudle, H *Tetrahedron* **1979**, *35*, 647,b) Baldwin, J E , Harwood, L M , Lombard, M J *Tetrahedron* **1984**, *40*, 4363

27 Scheeren, J W *Recl Trav Chim Pays-Bas* **1986**, *105*, 71-84, Aben, R W M , Smit, R Scheeren, J W *J Org Chem* , **1987**, *52*, 365-370, Hofstraat, R Thesis, University of Nijmegen, **1987**

CHAPTER 7

Lewis Acid Catalyzed Diels-Alder Reactions of 2-Cyclohexenones with Functionalized Dienes

7.1 Introduction

The design and development of chiral Lewis acid catalysts for asymmetric Diels-Alder reactions has been mainly focused on the reaction of simple α,β-enals (e g methacrolein, 2-bromoacrolein) with simple dienes (e g cyclopentadiene, isoprene)[1] This has resulted in a number of interesting applications, e g the synthesis of prostaglandines (Figure 1) The question remains open whether this methodology can be applied to the asymmetric Diels-Alder reaction of 2-cyclohexenones which has shown to be a powerful and straightfoward method to synthesize sesquiterpenes, diterpenes, steroids, and alkaloids[3] Until now chiral Lewis acid catalysts have not been applied to these Diels-Alder reactions of 2-cyclohexenones

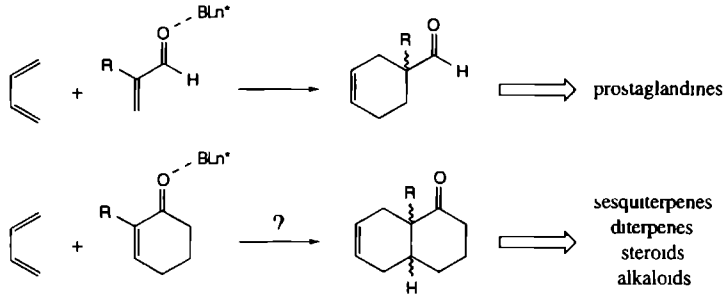


Figure 1 Chiral Lewis acid catalyzed asymmetric Diels-Alder reactions

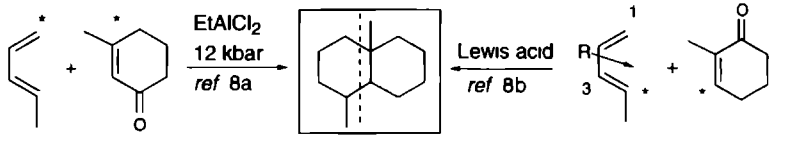
In this chapter the first results are presented on the application of (chiral) Lewis acids in Diels-Alder reactions of 2-cyclohexenones with oxygenated functionalized dienes aimed at the synthesis of the eudesmane sesquiterpene skeleton

Eudesmane sesquiterpenes including both 6,12- and 8,12-olide moieties make up a group of natural products which are widely present in the plant kingdom[4] These natural products have aroused much interest because of their wide spectrum of biological properties, particularly the cytotoxic and antitumour activity associated with the α-methylene γ-lactone group[5a] Recent reports also ascribe antifeedant properties to some sesquiterpene lactones[5b] Numerous total and partial

syntheses of members of this class of compounds, based on various synthetic strategies, e g the Robinson annelation, the carbon atom insertion bicycloannulation (CAIB), and the photocycloaddition of cyclobutenes to chiral enone monoterpenes have been published[6]

Conceptually, the regioselective Diels-Alder reaction of 2- or 3-methyl-cyclohexenones with functionalized dienes is the most simple strategy for eudesmane sesquiterpene synthesis The first Lewis acid catalyzed Diels-Alder reaction, using carvone as a dienophile, was reported by Harayama *et al* and led to β-eudesmol in an overall yield of 4%[7a] Although the yields of the reported achiral Lewis acid catalyzed reactions with alkyl substituted 1,3-butadienes were high[7b], only partly functionalized cycloadducts were obtained, which could be converted with difficulty to eudesmane type sesquiterpenes[7a] For convenient transformation of the cycloadducts to natural products the use of more functionalized dienes would be fruitful Recently, the high pressure and Lewis acid catalyzed Diels-Alder reaction of 3-methyl-2-cyclohexenone with simple dienes, e g (*E*)-piperylene was reported (*Scheme 1*) yielding regioselectively a *cis*-octalone with an angular methyl group[8a] Under the reaction conditions partial epimerization to the *trans*-octalones was observed

Scheme 1 Regioselective Diels-Alder strategy towards cis-decalin system with angular methyl group



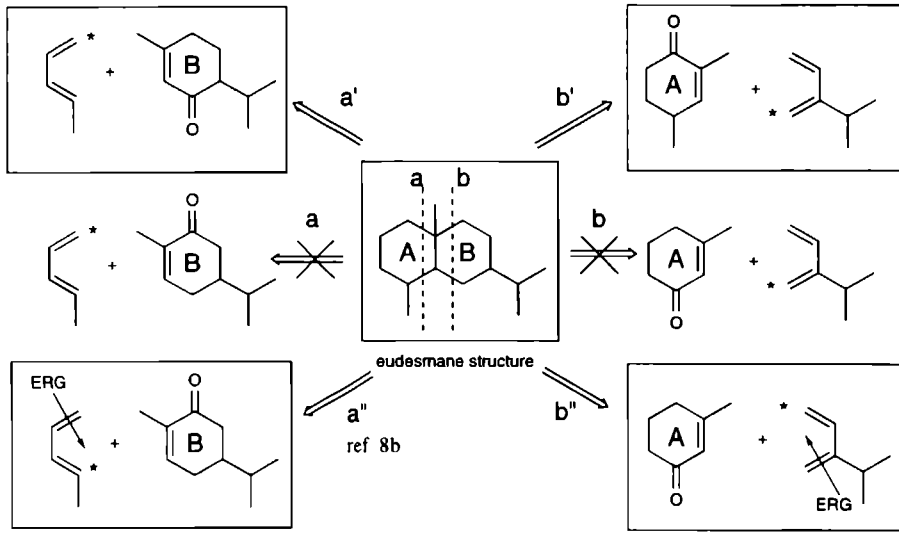
R = electronreleasing substituent at C(1) or/and C(3)

In principle, the desired cycloadducts with noreudesmane structure will also be accessible by a Lewis acid catalyzed regioselective Diels-Alder reaction of electron rich 1,3-pentadienes, having electron-releasing substituents at C(1) and/or C(3), with 2-methyl-2-cyclohexenone[8b]. Very recently Haaksma *et al* [8c] reported the $EtAlCl_2$-catalyzed Diels-Alder reaction of *S*(+) carvone with silyloxy dienes in a total synthesis of (+)-α-cyperone, showing the synthetic value of this strategy

In *Scheme 2* a brief retrosynthetic analysis for eudesmane sesquiterpenes is given, based on the regioselective Diels-Alder methodology The regioselectivity of the Diels-Alder reaction is controlled by the HOMO (Highest Occupied Molecular Orbital) coefficient of the diene (marked *) and the LUMO (Lowest Unoccupied Molecular Orbital) coefficient of the cyclohexenone, according to frontier molecular orbital theory[9] Route a, a', and a" represent the same reactions of 1,3-pentadienes with a methylated cyclohexenone B-ring Route b, b', and b" represent Diels-Alder reactions involving 2-substituted 1,3-butadienes with a methylated cyclohexenone A-ring Route a and b would give the wrong regiochemistry and are not suitable Route a', starting from piperylene and piperitone, and route b' starting from 2,4-dimethyl-2-cyclohexenone and 2-isopropyl 1,3-butadiene would afford a short convergent route to the eudesmane skeleton According to route a", 1,3-pentadienes with electron-releasing groups (ERG) on position 1 and/or 3 will also give a regioselective reaction with carvone[8], a commercially available monoterpene Route b" represents the

high-pressure/Lewis acid catalyzed Diels-Alder reaction of commercially available 3-methyl-2-cyclohexenone with 2-isopropyl-1,3-butadiene having electron-releasing groups (ERG) at position 1 and/or 3, for example 2-oxygenated 1,3-butadienes

Scheme 2 Strategies for the regioselective synthesis of eudesmane sesquiterpenes by Diels-Alder reactions



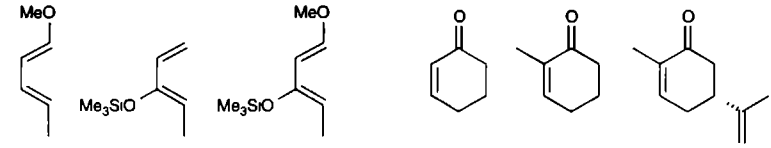
The extensive studies on Lewis acid catalyzed Diels-Alder reactions of 2-cyclohexenones with simple dienes by Taticchi *et al* [3] have revealed some characteristic features of these reactions A critical parameter is the complexation time, i e the time needed for the formation of the maximum concentration of the reactive Lewis acid-ketone complex prior to the addition of the diene The reaction time and product yield depend strongly on the quantity of catalyst employed, in general 25-50 mol% of catalyst and a complexation time of *ca* 40 min gave the best results The reactivity and *endo-exo* stereoselectivity depend on the C(2) substitution pattern In the presence of strong Lewis acids, e g $AlCl_3$, C(2)-unsubstituted 2-cyclohexenones are less reactive than 2-methyl-2-cyclohexenone but give almost exclusively *endo* addition (for example with (*E*)-piperylene) in contrast to the latter compound, which gives both *endo* and *exo* adducts[7c]

7.2 Results and discussion

7.2.1 Lewis acid catalyzed regioselective Diels-Alder reactions of electron-rich 1,3-pentadienes with 2-cyclohexenones (route a")

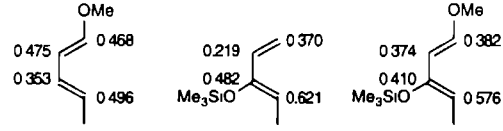
In order to study the regioselectivity of the Lewis acid catalyzed Diels-Alder reaction of 2-cyclohexenones with electron-rich 1,3-pentadienes and to show the generality of this approach (Scheme 2, route a), 1-methoxy-1,3-pentadiene **1**[10], 3-trimethylsilyloxy-1,3-pentadiene **2**[11], and 1-

methoxy-3-trimethylsilyloxy-1,3-pentadiene **3**[12] with 2-cyclohexenone **4**, 2-methyl-2-cyclohexenone **5**[13] and *R*(-)-carvone **6** were investigated cas reaction components both under high pressure and without pressure.



1 **2** **3** **4** **5** **6**

Computational studies of the regioselectivity of this type of Diels-Alder reaction (AM1 Hamiltonian MOPAC 6.01) show that for dienes **1**, **2** and **3** the highest HOMO-coefficient is present at C(4), indicating that the directing effect of a 1- and/or 3-oxy substituent predominates over a 4-alkyl substituent. Applying frontier molecular orbital (FMO) theory[9a] it can be calculated that the 2-cyclohexenones used in this study have their highest LUMO-coefficient located at the β–carbon of the enone system[9b]. Hence, the regioselectivity of the Diels-Alder reactions can be assigned in a highly predictable way.

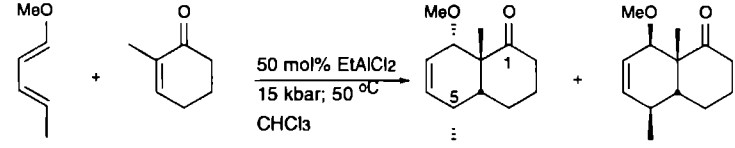


HOMO-energy(eV) -8.52 -8.65 -8.30

*Diels-Alder reactions of **1** with cyclohexenone **5***

The Diels-Alder reaction of diene **1** (*E,E*:*E,Z* = 2:1)[10d] with cyclohexenones **5** and **6** did not proceed under thermal conditions (2 days at 160 °C in toluene) or with Lewis acids like $AlCl_3$ in toluene at 70 °C[14]. The combination of Lewis acid ($EtAlCl_2$) and high pressure (15 kbar) was necessary to achieve a cycloaddition of **1** with **5** in chloroform at 50 °C. A 4:1 mixture of *endo/exo* adducts **7a** and **7b**[15] was isolated in 9% yield (*Scheme 3*). Under these conditions the mild Lewis acid catalyst $Eu(fod)_3$ did not catalyze the reaction.

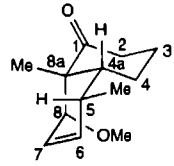
Scheme 3



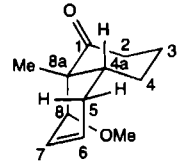
1 **5** **7a** **7b**

Recently, Fringuelli *et al.*[16] reported that the thermal Diels-Alder reactions of 1-methoxy-1,3-butadiene with 2-methyl-2-cyclohexenone and give cycloadducts in low yield displaying moderate *endo/exo* stereoselectivity. Analysis of the products by IR and ^1H- and ^{13}C-NMR spectroscopy showed that *endo*-adduct **7a** has a conformation similar to that of the corresponding *endo*-adduct **7c** (lacking the 5-Me substituent) as reported by Fringuelli *et al.*[16]. Introduction of the 5-Me group

causes : 1) an upfield shift of 5 ppm for the ^{13}C-signal of C-4 due to the γ-effect of the 5-Me; 2) shielding of C-4a and a 6 ppm upfield shift of the ^{13}C-signal of this carbon atom; 3) a stronger shielding of C-2 by the 8-OMe and a 4 ppm upfield shift of the ^{13}C-signal (Table 1, p. 132).



7a

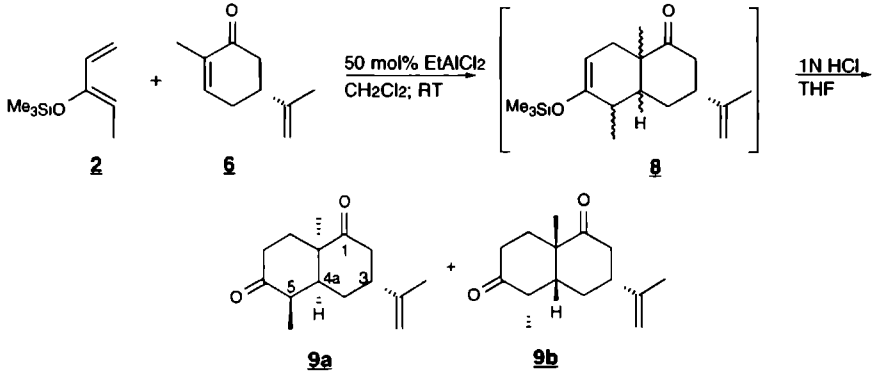


7c[16]

Diels-Alder reactions of **2** *with cyclohexenones* **4**, **5** *and* **6**

The Diels-Alder reaction of the more reactive diene **2** with *R*(-)-carvone[7] **6** was conducted in dichloromethane at room temperature using 50 mol% of $EtAlCl_2$ as a catalyst[17]. After 16 hours the cycloadduct **8** was hydrolyzed with 1N HCl in THF for 60 min. at 0 °C and the product was isolated as a 92 : 8 mixture of *anti-endo*- (**9a**) and *syn-endo*-adduct (**9b**) in 71% overall yield (*Scheme 4*). In contrast to the reported reaction of diene **2** with *S*(+)-carvone in toluene[8c] no epimerization of C-4 was observed for adduct **9a** under the employed reaction conditions[18]. The ^{1}H- and ^{13}C-NMR data of **9a** and **9b** (Table 1, p. 132) are in full agreement with the reported values for adducts of S(+)-carvone. Decoupling experiments with **9a** showed that the hydrogen at C-5, which appeared as a quintet at δ = 2.89 ppm, gives a quartet coupling with 5-Me (J = 6.7 Hz) and a doublet coupling with H-4a (J = 5.2 Hz). This indicates the presence of an axial-equatorial coupling for the angular proton and the proton at C-5 and thus a cis-orientation for the two hydrogens. The relative configuration of **9b** was characterized, in the same way, by a quintet located at ∂ = 2.94, $J_{H5,H4a}$ = 5.0 Hz.

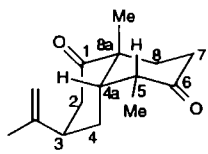
Scheme 4



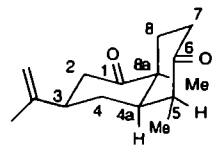
2 **6** **8** **9a** **9b**

The ^{1}H-NMR spectrum gave further information about the conformation of the adducts. The olefinic hydrogens of the isopropenyl group of **9a** appeared as separate singlets with a shift difference of 0.25 ppm, indicating that this group has an axial position. The predominant conformations of **9a** and **9b** are depicted below. Analysis of the carbon shifts in their ^{13}C-spectra gave additional information. The axial isopropenyl group in **9a** caused an upfield shift of *ca.* 5 ppm

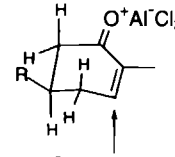
for C-4a because of a γ-effect The 1,3-diaxial interaction between the axial isopropenyl group and the angular hydrogen caused a γ-effect on C-3



9a



9b

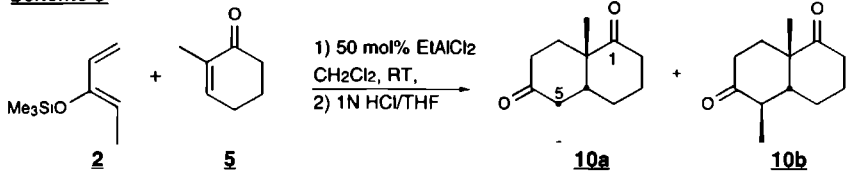


9c anti

The observed *anti* selectivity can be rationalized as shown in **9c** for the $AlCl_3$ catalyzed reaction of carvone with simple dienes[7b,c] The *endo*-diastereoselectivity is the result of stabilizing secondary orbital interactions in the transition state, assuming that repulsive effects between the diene and the dienophile in the *endo* transition state are negligible

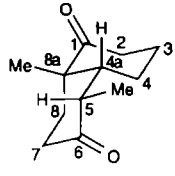
The cycloaddition of diene **2** with 2-methyl-2-cyclohexenone **5** catalyzed by 50 mol% $EtAlCl_2$ in dichloromethane at room temperature and subsequent hydrolysis of the silyl enol ether cycloadduct yielded a 7 3 mixture (GLC) of *endo*-**10a** and *exo*-adduct **10b** (*Scheme 5*) After separation and isolation of the two diastereoisomers by chromatography, in 23% and 15% isolated yield respectively, the conformation of the products was determined by ^1H- and ^{13}C-NMR spectroscopy and decoupling experiments

Scheme 5

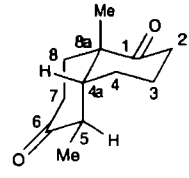


2 **5** **10a** **10b**

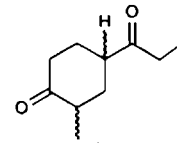
In the ^1H-NMR spectrum of **10a** the C-5 proton at δ 2 92 ppm appeared as a quintet with couplings $J_{H5,5\text{-}Me}$ = 6 3 Hz and $J_{H5,H4a}$ = 5 0 Hz, indicating an axial-equatorial coupling and thus a *cis-endo* orientation of the two hydrogens H5 and the angular proton H4a In the case of compound **10b** the proton H5 appeared as a sextet with couplings $J_{H5\,5\,Me}$ = 6 Hz and $J_{H5,H4a}$ = 14 Hz This indicates an axial-axial coupling for the angular proton and the proton at C-5 and hence a *trans*-coplanar orientation of the two hydrogens Further information about the conformation of the cycloadducts was obtained from ^{13}C-NMR spectroscopy (see Table 1) In compound **10a** the angular methyl group 8a-Me is located at the site *peri* to the C-1 keto function and is shielded by a nonbonded interaction with the carbonyl oxygen giving an upfield shift of ca 7 ppm For the *exo*-product **10b** the 8a-Me group causes a γ-effect on C-4 leading to an upfield shift of *ca* 3 ppm for the latter carbon atom



10a



10b



11

When the above mentioned $EtAlCl_2$-catalyzed reaction was performed under high pressure (14 kbar) in dichloromethane for 14 hours the yield of the cycloaddition was not improved (39% overall yield, *endo/exo* ratio = 1 1) and some dimerisation of the diene was observed The *exo*-adduct **10b** and the dimer **11** were isolated after chromatography and were characterized by ^1H- and ^{13}C-NMR spectroscopy (Table 1)

The Diels-Alder reaction of diene **2** with cyclohexenone **4** catalyzed by 50 mol% of $EtAlCl_2$ in dichloromethane at roomtemperature for 17 hours, followed by hydrolysis of the silyl enol ether yielded a 1 1 mixture of *endo*- and *exo*-adducts **12a** and **12b** (*Scheme 6*) After a difficult separation of the products by MPLC only the *exo*-adduct **12b** could be isolated in a pure form (15% isolated yield) This compound was further analyzed by ^1H- and ^{13}C-NMR (Table 1)

Scheme 6

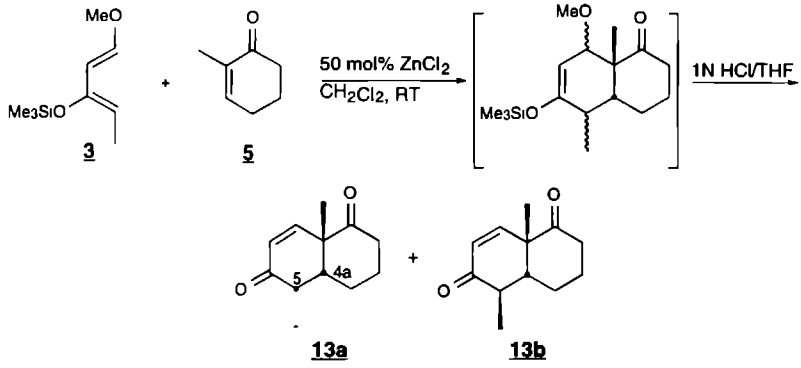
2 **4** **12a** **12b**

The proton at C-5 appeared at δ 2 64 ppm as a sextet with coupling constants $J_{H5,5\ Me}$ = 6 6 Hz and $J_{H5\ H4a}$ = 13 6 Hz, indicating an axial-axial coupling between the angular proton and the proton at C-5 and thus a *trans*-coplanar orientation of the two protons ^{13}C-NMR showed that C-4 is not shielded by an angular methyl group as was the case in **10b** As the 5-Me carbon atom had a similar ^{13}C-shift as the 5-Me in **10b**, *exo*-adduct **12b** must have the same conformation as **10b**

*Diels Alder reactions of **3** with cyclohexenones **4** and **5***

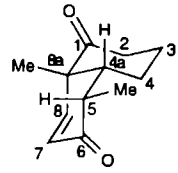
In view of the high reactivity of 1-methoxy-3-trimethylsilyloxydiene **3** and its sensitivity to acid, the use of strong Lewis acids catalysts, e g $AlCl_3$ and $EtAlCl_2$, is precluded for reactions with this compound The Diels-Alder reaction of **3** with cyclohexenone **5** was therefore carried out in the presence of 50 mol% of $ZnCl_2$ as catalyst in dichloromethane at room temperature The primary *endo*- and *exo*-cycloadducts were not isolated The mixture was quenched after 1 hour with diluted acid in THF to yield a 1 2 mixture of α,β-unsaturated ketones **13a** and **13b** (*Scheme 7*)

Scheme 7

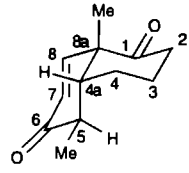


3 **5** **13a** **13b**

The product **13b** (23% isolated yield after chromatography) was analyzed by ^{1}H- and ^{13}C-NMR spectroscopy Decoupling experiments on **13b** made the proton at C-5, located at δ 2 25 ppm, appear as a sextet with coupling constants of $J_{H5,5\text{-}Me}$ = 6 6 Hz and $J_{H5\ H4a}$ = 12 6 Hz, indicating a *trans*-coplanar relationship for the angular protons H4a and H5 The ^{13}C-NMR signal of the 8a-Me group in *endo*-adduct derived ketone **13a** (deduced from the mixture of **13a** and **13b**) showed an upfield shift of *ca* 5 ppm, due to shielding by the carbonyl oxygen of the keto function at C-1 These data indicate that the hydrolyzed adducts probably have conformations as depicted below



13a



13b

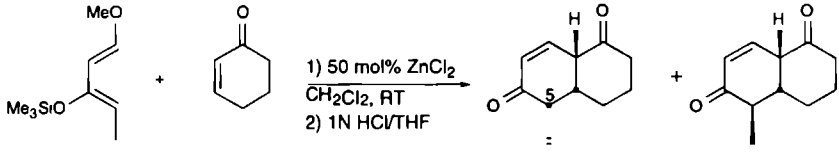
Table 1 ^{13}C Chemical Shifts of Bicyclic Ketones **7**-**14**[a]

carbon atom	Compound								
	7a	**9a**	**9b**	**10a**	**10b**	**12b**	**13a**	**13b**	**14a**
C-1	214 6	213 9	213 1	213 7	214 1	212 7	211 8	213 6	210 7
C 2	37 1	40 7	42 1	37 7	38 7	41 4	39 8	38 0	38 2
C 3	23 3	39 4	44 3	22 3	20 9	21 6	22 3	21 4	24 1
C 4	23 9	24 2	27 6	25 1	22 6	25 2	24 4	22 6	25 8
C-4a	32 6	46 6	51 8	44 1	43 8	44 8	42 2	41 4	41 6
C-5	46 0	43 3	44 0	52 8	52 7	49 1	50 3	49 0	52 8
5-Me	20 3	11 8	12 0	12 0	11 2	11 1	12 2	10 8	11 6
C-6	134 2	211 7	211 1	211 4	213 1	211 2	200 7	200 6	200 7
C-7	124 1	37 6	37 5	37 2	37 5	38 1	128 7	127 6	131 0
C-8	76 0	32 6	32 2	32 2	35 0	27 3	149 0	153 1	141 0
C-8a	52 8	49 1	49 0	49 7	49 2	47 5	52 7	52 1	44 7
8a-Me	20 6	19 2	19 0	19 1	26 5	-	20 2	25 3	-
8-OMe	57 4	-	-		-	-		-	-
C 9	-	146 0	146 9		-	-		-	-
C-10	-	112 8	110 9	-	-	-		-	
C-11	-	21 8	20 2		-	-		-	-

[a] in ppm recorded in $CDCl_3$

The Diels-Alder reaction of diene **3** with cyclohexenone **4** was performed with 50 mol% of $ZnCl_2$ as catalyst in dichloromethane at room temperature After 1 hour the reaction was quenched with 1N HCl to give a mixture of hydrolyzed *endo*- and *exo*-adducts **14a** and **14b**[19] (*Scheme 8*) These isomers could not be separated completely by chromatography, only **14a** was obtained pure in 13% isolated yield From a comparison of the ^{13}C-chemical shifts of **14a** with those of *endo*-adduct **13a**, it was concluded that cycloadduct **14a** is the *endo*-isomer

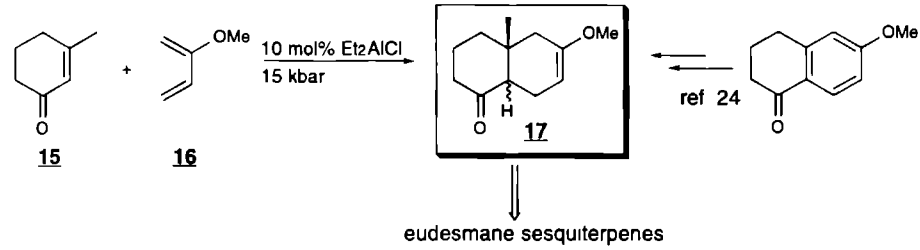
Scheme 8



7.2.2 High Pressure-Lewis Acid Catalyzed Diels-Alder Reaction of 3-Methyl-2-Cyclohexenone with 2-Silyloxydienes (route b"). Synthesis of a Versatile Synthon for Eudesmane Sesquiterpenes

The application of high pressure (12-15 kbar) to the Lewis acid catalyzed Diels-Alder reactions of simple dienes with 3-methyl-2-cyclohexenone **15**, a poor dienophile which for a long time was considered as being unreactive in Diels-Alder reactions[23], has been reported recently[8a] Some efforts have been made in developing general routes for the synthesis of eudesmane sesquiterpenes starting from decalone **17**[24], which can be derived from 5-methoxy-tetralone via a multistep sequence in a low overall yield (*ca* 10%) We envisaged the possibility of constructing this versatile synthon via a high-pressure and Lewis acid catalyzed regioselective Diels-Alder reaction of 3-methyl-2-cyclohexenone with 2-methoxy-1,3-butadiene **16**[25] (*Scheme 9*) according to route b" (section 7 1 of this chapter)

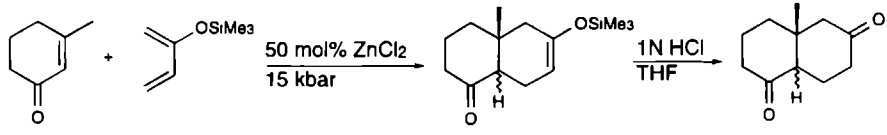
Scheme 9



Unfortunately, rapid polymerization of the diene **16** under the reaction conditions (10 mol% Et_2AlCl, 15 kbar) prevented the formation of **17** We next turned our attention to the use of 2-silyloxydienes, which react more rapidly and regioselectively with other dienophiles than the corresponding 2-alkoxy dienes[26] The reaction of 3-methyl-2-cyclohexenone **15** with silyloxy diene **18**[27] catalyzed by 50 mol% $ZnCl_2$ at 15 kbar high pressure in dichloromethane at room temperature gave complete

conversion of the cyclohexenone after 2 days (*Scheme 10*) After hydrolysis of the cycloadducts **19** (not isolated) and subsequent chromatography, the diketones **20** could be isolated in *ca* 10% yield from the reaction mixture, which contained many unidentified by-products Other Lewis acids with variable acidity, e g Et_2AlCl and $EtAlCl_2$, did not improve the yield, due to the lability of the trimethylsilyloxy group

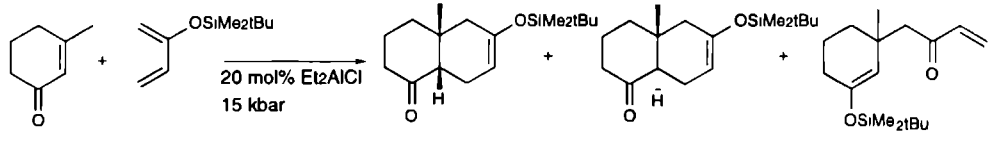
Scheme 10



18 **19** **20**

The hydrolytically more stable diene **21**[28] reacted with 3-methyl-2-cyclohexenone in the presence of 20 mol% of Et_2AlCl as catalyst at 15 kbar and at room temperature (*Scheme 11*) After 16 hours the reaction mixture was poured into ice-water and purified by chromatography The primary Diels-Alder *cis*-cycloadduct **22** was isolated together with the epimeric *trans*-adduct **23**[8a] and Michael adduct **24** in a ratio of 6 3 1 and an overall yield of 58%

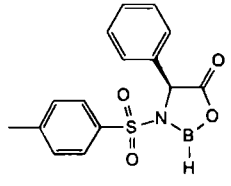
Scheme 11



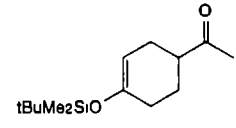
21 **22** **23** **24**

Under identical conditions the stronger Lewis acid $EtAlCl_2$ (20 mol%) gave only 20% yield Other less stronger Lewis acids, e g $ZnCl_2$ or (+)-Eu(hfc)$_3$, gave no reaction The stable, purified mixture of cis-**22** and trans-**23** (2 1) was smoothly transformed into the decalone **20** by treatment with 1 M TBAF in THF[29] for one hour at room temperature

In an attempt to introduce chirality in the product via a chiral Lewis acid catalyzed asymmetric Diels-Alder reaction of 3-methyl-2-cyclohexenone with silyloxy dienes the *L*-phenylglycine derived chiral oxazaborolidine **25**[30] was tested as suitable mild catalyst In a reaction of **15** with diene **18** catalyzed by 50 mol% of chiral Lewis acid **25** at 15 kbar the diketone **20** was isolated after hydrolysis and chromatographic purification (10% isolated yield) Hardly any enantioselectivity was observed (< 1% ee), as determined by LIS-NMR spectroscopy [31]



25

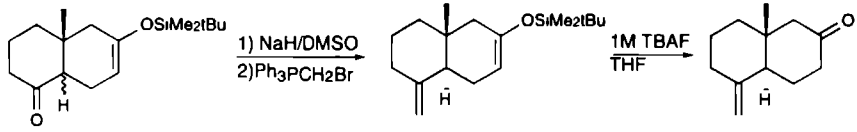


26

Although diene **21** is expected to be more stable towards acids than diene **18**, it gave under the same conditions surprisingly no cycloaddition with the cyclohexenone Instead, dimeric compound **26** was isolated as the only product Apparently, in the case of **21** more steric hindrance is present in the transition state between the chiral oxazaborolidine complexed cyclohexenone and the bulky *tert*-butyldimethyl-silyloxy group of **21**, than in the case of **18** which contains a smaller trimethylsilyloxy group

For the synthesis of some eudesmane sesquiterpenes the introduction of an exocyclic methylene bond in the decalone structure is important[1,24] Simple Wittig reaction of the *cis/trans* mixture **22/23** using the NaH/DMSO-method[32] will afford the olefin **27** with concomitant enolic epimerization of the *cis*-octalone to the desired *trans*-octalone[23b] (*Scheme 12*) Deprotection of the silyl enol ether with TBAF will give the ketone **28**, a versatile intermediate in the total synthesis of some eudesmane sesquiterpenes[24] Alternatively, a Mukaiyama aldol condensation of silyl enol ether **27** with acetone equivalents, catalyzed by some Lewis acid (e g $TiCl_4$), will allow the introduction of an isopropyl equivalent, to obtain directly a protected eudesmane sesquiterpene

Scheme 12



22/23 **27** **28**

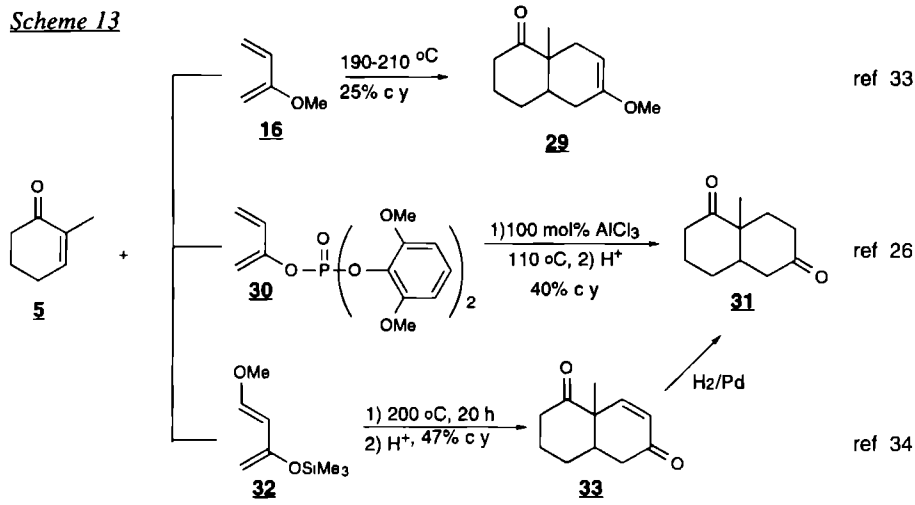
Given these perspectives we believe that the silyl enol ether **22/23** can be regarded as an equivalent of alkyl enol ether **17** which has proven to be a versatile intermediate for eudesmane synthesis The one-step synthesis of **22/23** via Diels-Alder methodology has great advantage over the low-yielding multi-step syntheses of **17** from 5-methoxytetralone[24] The introduction of chirality via a chiral Lewis acid catalyzed reaction remains a challenging goal

7.2.3 (Chiral) Lewis acid catalyzed Diels-Alder reaction of 2-methyl-2-cyclohexenone with 2-silyloxydienes (route b')

In order to explore the utility of route b' we decided to start our first experiments with 2-methyl-2-cyclohexenone (instead of 2,4-dimethyl-2-cyclohexenone) and a suitable diene, which allows the introduction of an isopropyl functionality after the Diels-Alder reaction In 1950 Nazarov *et al* [33] reported the thermal Diels-Alder reaction of 2-methoxy-1,3-butadiene **16** with 2-methyl-2-cyclohexenone **5** at 190-210 °C to give ca 25% yield of the cycloadduct **29** (based on reacted cyclohexenone) (*Scheme 13*) The chief obstacles to this reaction are dimerization and polymerization of the diene, even at lower temperatures Danishefsky *et al* [34] showed that the more reactive silyloxy diene **32** reacts under thermal reaction conditions (20 hours, 200 °C) with 2-methyl-2-cyclohexenone **5** to afford the diketone **31**, after catalytic hydrogenation of hydrolyzed cycloadduct **33** Compared to the R_3Si group, the $(RO)_2P(O)$ group can be viewed as being electron withdrawing and therefore

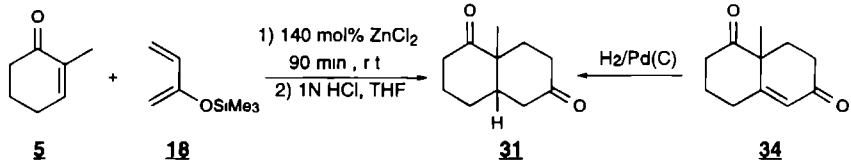
deactivating However, it was reported that the phosphate diene **30** reacts with 2-methyl-2-cyclohexenone **5** in refluxing toluene catalyzed by 100 mol% $AlCl_3$ to give after hydrolysis the bicyclic dione **31** in approximately 40% isolated yield[26] Under the same Lewis acid conditions silyloxy diene **18** failed to react, probably due to the instability of the diene.

Scheme 13



Siloxy dienes are often preferred in Diels-Alder reactions because of their superior regioselectivity and the greater versatility of the products For this reason diene **16** was not tested in our high pressure/Lewis acid catalyzed Diels-Alder strategy Our initial experiments were focused on the Lewis acid catalyzed Diels-Alder reaction of 2-methyl-2-cyclohexenone **5** with 2-trimethylsilyloxy-1,3-butadiene **18** (*Scheme 14*)

Scheme 14

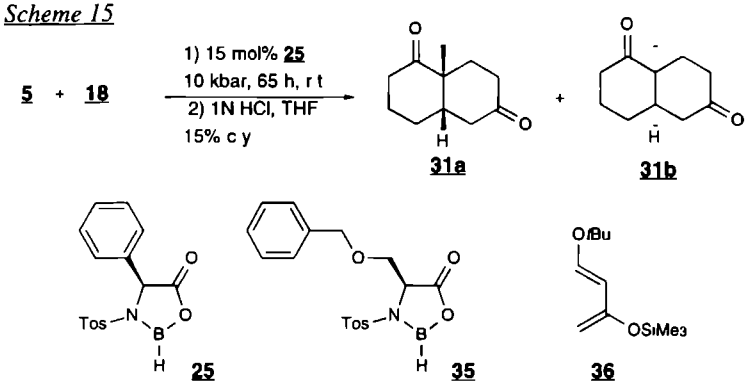


In the presence of 25 mol% of $EtAlCl_2$ or $ZnCl_2$ no cycloaddition occurred at room temperature and normal pressure. Probably the diene decomposed under influence of the Lewis acid, in contrast to the 3-silyloxy-1,3-pentadienes described in section 7 2 1 We found that the reaction proceeds when it is catalyzed by 140 mol% $ZnCl_2$ at room temperature in THF After 90 minutes the reaction mixture was hydrolyzed with 1N HCl and the diketone **31** was isolated in 26% yield after chromatographic purification An explanation for the fact that 140 mol% $ZnCl_2$ is required for the reaction may be that every cyclohexenone molecule must be activated by complexation with the Lewis acid before the diene is added to the reaction mixture In that case a fast cycloaddition reaction can compete with a fast decomposition of the diene In the presence of only 25 mol% of catalyst the competitive decomposition of the diene is probably faster than the cycloaddition The regiochemistry of the cycloadduct was established by comparison of the parent dione **31** with an authentic sample of **31**

prepared by catalytic reduction[26,35] of the Wieland-Miescher ketone **34**[36]

Next, the chiral oxazaborolidines **25** and **33**[30], *in situ* derived from BH_3-THF (1M in THF) and *L*-phenylglycine and *L*-serine(O-benzyl ether), respectively, were tested as chiral Lewis acid catalysts in the asymmetric synthesis of diketone **31** The reaction of 2-methyl-2-cyclohexenone **5** and diene **18** was carried out in the presence of 15 mol% of **25** at room temperature and at 10 kbar pressure (*Scheme 15*)

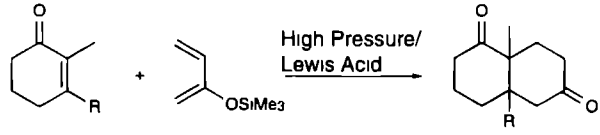
Scheme 15



After 65 hours the reaction mixture was hydrolyzed with acid to give after chromatographic purification a mixture of enantiomers of diketone **31** in 15% yield Unfortunately, the enantioselectivity of the reaction could be established by LIS-NMR spectroscopy using 20 mol% of (+)-Eu(hfc)$_3$ At elevated pressure (15 kbar) and temperature (50 °C) neither the yield (14% c y) nor the enantioselectivity were improved Under the same conditions 15 mol% of chiral oxazaborolidine **35** gave similar results The more reactive and bulky 1-*tert*-butoxy-3-trimethylsilyloxy-1,3-butadiene **36** gave no reaction (only dimerisation was observed) with cyclohexenone **5** in the presence of 15 mol% chiral oxazaborolidine **25** after 65 hours at 15 kbar and 50 °C only dimerisation was observed

Under high pressure the chiral Lewis acid catalyzed Diels-Alder reaction of 2-silyloxy-1,3-butadiene **18** might give higher reaction rates and chemical yields when it is carried out with cyclohexenones containing electron-withdrawing substituents in their β-position, e g. 2-methyl-3-chloro-2-cyclohexenone **37**[37] or 2-methyl-3-phenyl-sulphoxy-2-cyclohexenone **38**[38] (*Scheme 16*).

Scheme 16



In that case, the group R in **37** and **38**, which eventually provides access to the additional unit of unsaturation as in the Wieland-Miescher ketone **34**, must not compete with the carbonyl group in determining the regiochemistry of the cycloaddition reaction[39] Unfortunately, the 3-chloro- and the

3-phenylsulfinyl-2-methyl-2-cyclohexenones **37** and **38** failed to react with the silyloxy diene **18** under thermal (refluxing toluene) as well as high pressure and Lewis acid catalyzed conditions (15 kbar, 50 °C, 10-150 mol% $ZnCl_2$ or chiral catalysts **25** and **33**) Severe steric repulsion in the transition state between the 3-substituent of the 2,3-disubstituted cyclohexenone and the approaching diene probably prevents these compounds from undergoing a reaction at all

7.3 Conclusions

As reported in the literature, 2-cycloalkenones are dienophiles of low reactivity and their Diels-Alder reactions usually require drastic thermal conditions The coordination of the carbonyl function with Lewis acids dramatically increases the reactivity of the dienophile as well as the yield and selectivity of the cycloaddition reaction An alkyl group attached to C-2 of the cycloalkenones lowers the reactivity of the dienophile but the reaction with simple dienes generally proceeds in high yield under these Lewis-acid catalyzed conditions A methyl group at C-3 prevents the intermolecular cycloaddition, both under thermal and under Lewis-acid catalyzed conditions A combination of high pressure (12-15 kbar) and Lewis acid is therefore required for the less reactive 3-methyl-2-cyclohexen-1-one Although oxygenated dienes are more reactive than alkylated dienes, they are less stable in the presence of Lewis acids As a consequence, there will be a competition between the Lewis acid-catalyzed Diels Alder reaction and the decomposition of the diene From the results presented in this chapter the following conclusions can be drawn

1) For the weakly reactive pentadiene **1** a combination of Lewis acid catalysis and high pressure must be applied to allow this compound to give a Diels-Alder reaction with 2-cyclohexenones
2) The more reactive 3-silyloxy-1,3-pentadienes **2** and **3** react at room temperature with cyclohexenones in the presence of Lewis acid catalysts, e g $EtAlCl_2$ and $ZnCl_2$
3) In general, the isolated yields of the reactions are moderate, often due to the difficult separation of the *endo/exo* isomers but also because of the instability of the dienes used
4) The regioselectivity of the Diels-Alder reactions has been unambiguously determined by ^1H- and ^{13}C-NMR spectroscopy For the dienes **1**-**3** the directing effects of the 1- and 3-hetero substituents are more important than the directing effect of the methyl substituent
5) The *endo-exo* stereoselectivities of the reactions are moderate probably due to a competition between attractive secondary orbital interactions and steric repulsion in the transition state of the reaction between the diene and the dienophile
6) The most straightforward route to some eudesmane sesquiterpenes, so far, is the high pressure and Lewis acid catalyzed Diels-Alder reaction of 3-methyl-2-cyclohexen-1-one with 2-TBDMSO-butadiene
7) Although only a first start has been made to use chiral oxazaborolidines as catalysts in the asymmetric Diels-Alder reactions of 2-cycloalkenones, it can already be concluded that for an effective application of the Diels-Alder methodology to natural product syntheses, e g eudesmane sesquiterpene synthesis, the development of stronger chiral Lewis acid catalysts is a prerequisite

7.4 Experimental Section

Dichloromethane was dried and distilled on CaH_2 All reactions were carried out under dry nitrogen or argon atmosphere ^{1}H-NMR spectra and ^{13}C-NMR were recorded on a Varian EM 390 (90 MHz, CW), a Bruker AM-100 (100 MHz, FT) or a Bruker AM-400 (400 MHz, FT) spectrometer with TMS as internal standard Decoupling experiments were run with DEPT 135 IR spectra were run on a Perkin-Elmer 298 spectrophotometer Mass spectra were measured with a Varian SM1-B double focussing mass spectrometer or with a VG 7070E mass spectrometer Gas chromatography was performed on a Hewlett-Packard 5710A GLC-instrument equipped with a capillary HP cross linked methyl silicone (25 m x 0 31 mm) column Products were purified by flash -chromatography, an Miniprep LC instrument (Jobin Yvon) with Merck silicagel 60H as stationary phase, or a Chromatotron (Model 7924T, Harrison Research) with silicagel 60 PF_{254} (cont gypsum) as stationary phase Mixtures of ethyl acetate/n-hexane (1 / 6-10, v/v) were used as eluent The high pressure apparatus which was used has been described before[21]

Lewis acid catalyzed Diels-Alder reactions of 2-cyclohexenones (General Procedure)
A solution of 100 mg (*ca* 1 mmol) of a 2 cyclohexenone in 5 ml dichloromethane was mixed with 0 5 mmol $EtAlCl_2$ (0 5 ml of a 1 M solution in hexane) under an atmosphere of dry nitrogen The mixture was stirred for 40 min (complexation time) at room temperature Then 3 mmol of a diene was added and the mixture was stirred at room temperature After the cyclohexenone had been completely converted (checked by GLC) the reaction mixture was poured onto ice-water and extracted twice with diethyl ether (50ml) The organic layers were dried with Na_2SO_4 The residue obtained after evaporation of the solvent under reduced pressure, was further purified by chromatography and analyzed by GLC, IR and NMR spectroscopy For high pressure conditions the reaction mixture was placed in a 8 ml teflon ampule and a pin-point radical inhibitor was added Dichloromethane was added until the ampule was completely filled The ampule was closed and kept under 12-15 kbar pressure for the reported time After depressuring, the reaction mixture was poured out into ice-water and worked up as described above

8-Methoxy-5,8a-dimethyl-3,4,4a,5,8,8a-hexahydro-2H-naphtalen-1-one 7
After separation on a chromatotron (eluent ethyl acetate/n-hexane = 1/7, v/v) the product was isolated as a 4 1 mixture of **7a** and **7b** in 9% yield as an oil IR (cm $^{-1}$) 1720 (C=O), 1620 (C=C) ^{1}H-NMR δ (ppm) 5 91 (0 8H, m, $J_{H6\,H7}$ = 10 1 Hz, H6-endo), 5 80 0 2H, m, H6-exo, 5 63 0 8H, dd, $J_{H7\,H6}$ = 10 1 Hz, $J_{H7\,H8}$ = 3 0 Hz, H7-endo, 5 50 0 2H, m, $J_{H7\,H8}$ = 10 0 Hz, H7-exo, 4 10 0 2H, d, $J_{H8\,H7}$ = 10 0 Hz, H8-exo, 3 95 0 8H, d, $J_{H8\,H7}$ = 3 8 Hz, H8 endo, 3 36 2 4H, s, 8-OMe-endo, 3 31 0 6H, s 8-OMe-exo, 2 57 1H, m, H5, 2 30 1H, m, H4a, 2 25-1 75 3H, m, H2, H3 and H4a, 1 29 2 4H, s, 8a-Me-endo, 1 26 0 6H, s, 8a Me-exo, 1 06 2 4H, d, $J_{5\,Me,H5}$ = 7 2 Hz, 5-Me-endo, 1 00 0 6H, d, $J_{5\,Me\,H5}$ = 7 5 Hz, 5-Me-exo For ^{13}C-NMR chemical shifts see Table 1 Mass 208 (M^+), 193, 185, 175, 165, 149, 123, 107 HRMS calcd (M^+) m/e 208 1463, found m/e 208 1463

(3R,4aS,5R,8aR)-3-Isopropenyl-5,8a-dimethyl-hexahydro-naphtalene-1,6-dione 9a
The oily product was isolated as a 92 8 mixture of *anti-endo* **9a** and *syn-endo* **9b** in an overall yield of 71% All physical data agreed well with literature data[8c] IR (cm $^{-1}$) 1710 (C=O), 1660 (C=C) ^{1}H-NMR δ (ppm) 1 01 (d, J = 6 7 Hz, 3H), 1 45 (s, 3H), 1 71 (s, 3H), 1 10-2 75 (m, 10H), 2 89 (quintet, $J_{H5\ 5\ Me}$ = 6 7 Hz, $J_{H5,H4a}$ = 5 2 Hz), 4 63 (s, 1H), 4 88 (s, 1H) For ^{13}C-NMR chemical shifts see Table 1 Mass 234 1 (M^+), 191, 177, 163, 150, 149, 137 HRMS calcd (M^+) m/e 234 1619, found m/e 234 1619 **(3R,4aR,5S,8aS)-3-Isopropenyl-5,8a-dimethyl-hexahydro-naphtalene-1,6-dione 9b** ^{1}H-NMR δ (ppm) 1 05 (d, J = 6 7 Hz, 3H), 1 48 (s, 1H), 1 72 (s, 3H), 1 1-2 75 (m, 10H), 2 92 (quintet, J = 6 7 Hz, 1H), 4 75 (d, J = 9 Hz, 1H) HRMS calcd (M^+) m/e 234 1619, found m/e 234 1619

5,8a-Dimethyl-hexahydro-naphtalene-1,6-dione 10
The hydrolyzed isomers *endo*-**10a** and *exo*-**10b** were obtained as a 7 3 mixture (GLC) The two isomers were separated with a chromatotron (eluent ethyl acetate/n-hexane = 1/7, v/v) and were isolated in 23 and 15% yield, respectively *endo*-**10a** oil, IR (cm $^{-1}$) 1710 (C=O) ^{1}H NMR δ (ppm) 2 92 1H, quintet, $J_{H5\ 5\ Me}$ = 6 3 Hz, $J_{H5,H4a}$ = 5 0 Hz, H-5, 2 64-1 22 11H, m, H-2, H-3, H-4, H-4a, H-7 and H-8, 1 49 3H, s, 8a-Me, 1 03 3H, d, $J_{5\ Me\ H5}$ = 6 3 Hz, 5-Me For ^{13}C NMR chemical shifts see Table 1 Mass 194 (M^+), 166, 151, 137, 127, 111, 110 HRMS calcd (M^+) m/e 194 1307, found m/e 194 1306 *exo*-**10b** IR (cm $^{-1}$) 1710 (C=O) ^{1}H-NMR δ (ppm) 2 67 1H, sextet, $J_{H5\ 5\ Me}$ = 6 Hz, $J_{H5\ H4a}$ = 14 Hz, H-5, 2 60-1 75 11H, m, H-2, H-3, H-4, H-4a, H-7 and H-8, 1 30 3H, s, 8a-Me, 1 00 3H, d, $J_{5\ Me,H5}$ = 6 Hz, 5-Me Mass 194 (M^+), 166, 151, 137, 127, 110 HRMS calcd (M^+) m/e 194 1307, found m/e 194 1306

2-Methyl-4-propionyl-cyclohexanone 11
Oil, ^{1}H-NMR δ (ppm) 1 05 (3H, d, J = 6 5 Hz, 2-Me), 1 07 (3H, t, J = 7 2 Hz, H-9), 1 48-2 95 (8H, m, H 2, H-3, H-4, H-5, H-6), 2 54 (2H, q, J = 7 2 Hz, H-8) ^{13}C-NMR δ (ppm) 7 6 (C-9), 14 3 (2-Me), 29 2 (C-5), 34 1 (C-3), 37 3 (C-8), 40 2 (C-6), 43 7 (C 4), 49 0 (C-2), 211 2 (C-7), 212 1 (C-1)

5-Methyl-hexahydro-naphtalene-1,6-dione 12
The crude reaction mixture (GLC analysis *endo*-**12a** / *exo*-**12b** = 1/1)was purified by MPLC using flash" silica gel (Merck 200 mesh) using as eluent ethyl acetate/*n*-hexane = 1/10 (v/v) Only *exo*-**12b** was isolated as a pure compound in 15% yield *exo*-**12b** oil, IR (cm $^{-1}$) 1710 (C=O) ^{1}H-NMR δ (ppm) 2 76 1H, m, H-8a, 2 62 1H, sextet, $J_{H5,5\ Me}$ = 6 5 Hz, $J_{H5,H4a}$ = 13 6 Hz, H-5, 2 55-1 15 11H, m, H-2, H-3, H-4, H-4a, H-7 and H-8, 1 01 3H, d, $J_{5\ Me\ H5}$ = 6 5 Hz, 5-Me For ^{13}C-NMR chemical shifts see Table 1 Mass 180 (M^+), 152, 149, 149, 123, 113, 97 HRMS calcd (M^+) m/e 180 1150, found m/e 180 1156

5,8a-Dimethyl-2,3,4,4a,5,8a-hexahydro-naphtalene-1,6,-dione 13
A 1 2 mixture of *endo*-**13a** and *exo*-**13b** was isolated after chromatography Pure *exo*-**13b** was

isolated in 23% yield by separation on a Chromatotron using ethyl acetate/n-hexane = 1/7 (v/v) as eluent Oil, IR (cm $^{-1}$) 1710 (C=O), 1680 (C=O), 1600 (C=C) ^{1}H-NMR δ (ppm) 1 03 (3H, d, J = 6 6 Hz, 5-Me), 1 43 (3H, s, 8a-Me), 1 10-2 65 (8H, m), 2 25 (quintet, $J_{H5,5\ Me}$ = 6 6 Hz, $J_{H5,H4a}$ = 12 6 Hz, 1H, H-5), 5 98 (1H, d, J = 10 2 Hz, H-7), 6 71 (1H, d, 10 2 Hz, H-8) For ^{13}C-NMR chemical shifts see Table 1 Mass 192 (M^+), 164, 149, 135, 123, 109 HRMS calcd (M^+) m/e 192 1150, found m/e 192 1148 Physical data of *endo*-**13a** (deduced from the mixture of *endo*-**13a** and *exo*-**13b**) IR (cm $^{-1}$) 1710 (C=O), 1680 (C=O), 1600 (C=C) For ^{13}C-NMR chemical shifts see Table 1

5-Methyl-2,3,4,4a,5,8a-hexahydro-naphtalene-1,6-dione 14

The *endo* product **14a** was isolated (13% yield) after chromatography as an oil IR (cm $^{-1}$) 1715 (C=O), 1685 (C=O), 1600 (C=C) ^{1}H-NMR δ (ppm) 1 13 (3H, d, $J_{5\ Me\ H5}$ = 6 9 Hz, 5-Me), 1 20-2 78 (9H, m), 6 14 (1H, d, $J_{H7\ H8}$ = 9 9 Hz, H-7), 6 27 (1H, dd, $J_{H8\ H7}$ = 9 9 Hz, $J_{H8\ H8a}$ = 2 1 Hz, H8) For ^{13}C-NMR chemical shifts see Table 1 Mass 179 (M^+), 164, 149, 135, 123, 109 Calcd (M^+) m/e 178 0994 Found m/e 178 0990

4a-Methyl-hexahydro-naphtalene-1,6-dione 20

Treatment of the crude silyl enol ether **19** (not isolated) with 1N HCl in THF (1 hr, 0 °C) afforded the crude diketone **20** which was purified by chromatography on a Chromatotron, eluent ethyl acetate /*n*-hexane = 1 / 8 (v/v) Yield 10%, Oil, IR (cm $^{-1}$) 1705 400 MHz ^{1}H-NMR δ (ppm) = 1 11 (3H, s, 4a-Me), 1 60-2 59 (13H, m, H-2, H-3, H-4, H-5, H-7, H-8, H 8a) ^{13}C NMR δ (ppm) = 211 5 (C-1, C=O), 211 3 (C-6, C=O), 49 5 (CH2), 43 6 (C-4a), 40 4 (CH2), 37 8 (CH2), 37 2 (CH2), 29 6 (C-8a), 28 1 (4a-Me), 22 2 (CH2), 21 8 (CH2) HRMS (rel int) 181 (M^+ +1, 15), 180 (M^+, 100), 165 (15), 147 (12), 137 (22), 124 (68), 111 (79) Peak match Calcd 180 11503 Found 180 11501

***cis*-4a-Methyl-6-*tert*-butyldimethylsilyloxy-3,4,4a,5,8,8a-hexahydro-2H-naphtalen-1-one 22**

GLC/MS analysis of the reaction mixture showed the presence of three compounds with equal mass corresponding to the cycloadduct This indicates that except the *cis*-cycloadduct **22** also the epimerized *trans*-**23** and the Michael adduct **24** was formed The primary Diels-Alder *cis*-cycloadduct **22** was isolated together with the epimeric *trans*-adduct **23**[8a] and the Michael adduct **24** in a ratio of 6 3 1 and a overall yield of 58% 400 MHz ^{1}H-NMR δ (ppm) = 0 10 6H, s, 2x CH_3-Si, 0 90 9H, s, *t*-Bu-Si, 1 12 3H, s, 4a-Me, 1 26 2H, s, 5-CH_2, 1 69 2H, m, H-8, 1 88-2 50 7H, m, H-2, H 3, H-4 and H 8, 4 78 1H, d, J = 4 41 Hz, H-7 ^{13}C-NMR δ = (ppm) 211 4 (C-1, C=O), 147 4 (C-6), 53 0 (C 7), 46 0 (C-4a), 40 0 (C-5), 38 8 (C-8a), 37 4 (C-8), 36 5 (C-2), 28 3 (C-4), 25 6 (*t*-Bu-Si), 22 5 (C-3), 20 6 (4a-Me), 17 9 (C-Si), -4 4 (Me-Si), -4 6 (Me-Si) HRMS Mass (rel int) 295 (M^+ +1, 11), 294 (M^+, 44), 279 (15), 261 (12), 237 (42), 224 (10), 181 (10), 147 (19), 145 (25), 129 (48) ***trans*-4a-Methyl-6-*tert*-butyldimethyl-silyloxy-3,4,4a,5,8,8a-hexahydro-2H-naphta-len-1-one 23.** oil, 400 MHz ^{1}H-NMR δ (ppm) = 4 82 1H, d, J = 5 5 Hz, H-7 ^{13}C

NMR δ = (ppm) 212.0 (C-1, C=O), 148.0 (C-6), 52.7 (C-7), 45.5 (C-5), 41.7 (C-8), 41.0 (C-4), 39.9 (C-2), 38.8 (C-8a), 25.6 (*t*-Bu-Si), 22.7 (C-4), 20.5 (C-3), 18.4 (4a-Me), 17.9 (C-Si), -4.4 (2x Me-Si). HRMS Mass (rel. int.) 295 (M^+ +1, 10), 294 (M^+, 40), 279 (15), 261 (16), 237 (51), 181 (8), 147 (27), 145 (21), 129 (8). Treatment of a purified 2:1 mixture of **22** and **23** with 1M TBAF in THF (1 h, room temperature) gave pure diketone **20** (GLC), proving the chemical constitution of **22** and **23**.

8a-Methyl-hexahydro-naphtalene-1,6-dione 31[26,34]

Diketone **31** was isolated as a white solid (m.p. 66 °C; lit.[34] 65-66 °C) after purification by chromatography on a chromatotron, with eluent ethyl acetate/*n*-hexane (1/4, v/v) in 26% yield. IR (cm^{-1}) 1700 (C=O) 400 MHz ^{1}H NMR δ (ppm) 1.35 3H, s, 8a-Me; 1.40-2.61 13H, m, H-2, H-3, H-4, H-4a, H-5, H-7, H-8. ^{13}C NMR δ (ppm) 214.1 (C-1, C=O), 211.2 (C-6, C=O), 48.5 (C-8a), 46.0 (C-4a), 43.6 (C-5), 38.3 (C-7), 37.4(C-2), 33.6 (C-8), 26.6 (C-4), 23.9 (8a-Me), 22.9 (C-3). HRMS (rel. int.) $^m/_e$ 181 (M^+ +1, 2), 180 (M^+, 13), 149 (100), 123 (6), 111 (15). Peak Match Calcd. 180.11503 Found 180.11504. This diketone was identical to an authentic sample of diketone **31**, which was prepared by hydrogenation of the Wieland-Miescher ketone **34** over Pd/C[36].

7.5 References and Notes

1. For reviews see: a) Kagan, H.B.; Riant, O. *Chem. Rev.* **1992**, 1007; b) Lohray, B.B.; Bhushan, V. *Angew. Chem.* **1992**, *104*, 740; c) Deloux, L.; Srebnik, M. *Chem. Rev.* **1993**, *93*, 763-784; d) Maruoka, K.; Yamamoto, H. in "Catalytic Asymmetric Synthesis" , Ojima, I., Ed., VCH Weinheim, **1993**, Chapter 9, p. 413-440.
2. a) Corey, E.J.; Loh, T.-P. *J. Am. Chem. Soc* **1991**,*113*, 8966; b) Corey, E.J.; Cywin, C.L. *J. Org. Chem.* **1992**, *57*, 7372; c) Marshall, J.A.; Xie, S. *J. Org. Chem.* **1992**, *57*, 2987; d) Corey, E.J.; Guzman-Perez, A.; Loh, T.-P. *J. Am. Chem. Soc.* **1994**, *116*, 3611-3612.
3. For a review on Diels-Alder reactions of cycloalkenones see: Fringuelli, F.; Taticchi, A.; Wenkert, E. *Org. Prep. Proc. Int.* **1990**, *22*, 131-165. Recent reports : Minuti, L.; Radics, L.; Taticchi, A.; Venturini, L.; Wenkert, E. *J. Org. Chem.* **1990**, *55*, 4261-4265; Minuti, L.; Selvaggi, R.; Taticchi, A.; Gacs-Baitz, E.; Matchytka, D. *Synth. Commun.* **1991**, *21*, 2143-2155.
4. Roberts, J.S.; Bryson, I. *Nat. Prod. Rep.* **1984**, *1*, 105; Fraga, B.M. *Nat. Prod. Rep.* **1985**, *2*, 147; **1986**, *3*, 273; **1987**, *4*, 473; **1988**, *5*, 497; **1990**, *7*, 61; **1990**, *7*, 515.
5. a) Lee, K.H.; Hall, I.H.; Mar, E.C.; Starnes, C.O.; El Gebaly, S.A.; Waddell, T.G.; Hadgraft, R.I.; Ruffner, C.G.; Weider, I. *Science*, **1977**, *196*, 533; b) Van Beek, T.A.; De Groot, A. *Recl. Trav. Chim Pays-Bas* **1986**, *105*, 513.
6. Heatchcock, C.H. in *The total synthesis of natural products*, ApSimon, J., Ed.; John Wiley & Sons, New York, 1973, Vol. 2, Chapter 2; Heatchcock, C.H., Graham, S.L.; Pirrung, M.C.; Plavac, F.; White, C.T. in *The total synthesis of natural products*; ApSimon, J., Ed.; John

Wiley & Sons, New York, 1983, Vol 5, Roberts, J S *Nat Prod Rep* **1985**, *2*, 97 For some recent examples, see Banerjee, A K , Canudas-González, N , Corredor de Sepúlveda, M *J Chem Res (S)* **1992**, 310, Chen, X , Shao, S , Li, T , Li, Y *Synthesis* **1992**, 1061, Cardona, L , García, B , Giménez, J E , Pedro, J R *Tetrahedron* **1992**, *48*, 851, Li, Y , Chen, X , Shao, S , Li, T *Synth Commun* **1993**, *23*, 2457, Collado, I G , Alonso M S , Henández-Galán, R , Madero, J G , Massanet, G M *Tetrahedron* **1994**, *50*, 10531

7 a) Harayama, T , Cho, H , Inubushi, Y *Tetrahedron Lett* **1975**, 2693, *Chem Pharm Bull Jpn* **1977**, *25*, 2273, b) Angell, E C , Fringuelli, F , Pizzo, F , Porter, B , Taticchi, A , Wenkert, E *J Org Chem* **1985**, *50*, 4696-4698, c) Angell, E C , Fringuelli, F , Minuti, L , Pizzo, F , Porter, B , Taticchi, A , Wenkert, E *J Org Chem* **1986**, *51*, 2649, d) For an earlier report of a Diels-Alder reaction with carvone under thermal conditions see Nerdel, F , Dahl, H *Liebigs Ann Chem* **1967**, *710*, 90

8 a) Aben, R W M , Minuti, L , Scheeren, J W , Taticchi, A *Tetrahedron Lett* **1991**, *32*, 6445, b) The thermal Diels-Alder reaction of a 5-substituted 2-methyl-2-cyclohexenone was employed as strategy in the total synthesis of *dl*-chamaecynone, see Harayama, T , Cho, H , Inubushi, Y *Tetrahedron Lett* **1977**, *37*, 3273 The asymmetric Michael-type alkylation of chiral imines has been used in the enantioselective synthesis of (-)-geosmin and related noreudesmanes, see Revial, G *Tetrahedron Lett* **1989**, *30*, 4121-4124, c) Haaksma, A A , Jansen, B J M , de Groot, A *Tetrahedron* **1992**, *48*, 3121

9 a) For a discussion of the assignment of absolute regiochemistry in Diels-Alder reactions by the FMO-theory vs the reactivity modelling procedure' see Houk, K N *J Am Chem Soc* **1973**, *95*, 4092, Houk, K N , Strozier, R W *J Am Chem Soc* **1973**, 4094, Eisenstein, O , Lefour, J M , Anh, N T , Hudson, R F *Tetrahedron* **1977**, *33*, 523, Kahn, S D , Pau, C F , Overman, L E , Hehre, W J *J Am Chem Soc* **1986**, *108*, 7381 b) For a discussion of the regioselectivity of 2-cyclohexenones in Diels-Alder reactions see Angell, E C , Fringuelli, F , Minuti, L , Pizzo, F , Taticchi, A , Wenkert, E *J Org Chem* **1986**, *51*, 5177

10 For preparation methods and Diels-Alder reactions of 1-methoxy-1,3-pentadiene see a) Schmidt, C , Sabnis, S D , Schmidt, E , Taylor, D K *Can J Chem* **1971**, *49*, 371, b) Kelly, T R , Goerner, R N , Jr , Gillard, J W , Prazak, B K Tetrahedron Lett **1976**, *43*, 3869, c) Martin, S F , Garrison, P J *Tetrahedron Lett* **1977**, *44*, 3875, d) Broekhuis, A A , Scheeren, J W , Nivard, R J F *Recl Chim Pays-Bas* **1979**, *99*, 6, e) Terada, M , Mikami, K , Nakai, T *Tetrahedron Lett* **1991**, *32*, 935

11 For preparation methods of 3-trimethylsilyloxy-1,3-pentadiene see a) Gerard, C , Amice, P , Barnier, J P , Conia, J M *Tetrahedron Lett* **1974**, 3329, b) Danishefsky, S , Yan, C F *Synth Commun* **1978**, *8*, 211, c) Miller, R D , McKean, D R *Tetrahedron Lett* **1979**, 2305, d) Bell, V L , Holmes, A B , Hsu, S -Y , Mock, G A , Raphael, R A *J Chem Soc , Perkin Trans I* **1986**, 1507, e) Cazeau, P , Duboudin, F , Moulines, F , Babot, O , Dunogues, J *Tetrahedron* **1987**, *43*, 2089 For the regiochemistry of 3-trimethylsilyloxy-1,3-pentadiene in thermal Diels-Alder reactions see f) Mock, G A , Holmes, A B , Raphael, R A *Tetrahedron Lett* **1977**, 4539, g) Ackland, D J , Pinhey, J T *J Chem Soc Perkin Trans I*

1987, 2689, h) Boisvert, L , Brassard, P *J Org Chem* **1988**, *53*, 4052, i) Kraus, G A , Liras, S *Tetrahedron Lett* **1989**, *30*, 1907,

12 For preparation and Diels-Alder reactions of 1-methoxy-3-trimethylsilyloxy-1,3-pentadiene see a) ref 3 , b) Danishefsky, S , Yan, C -F , Singh, R K , Gammill, R B , McCurry, P M , Jr , Fritsch, N , Clardy, J J Am Chem Soc **1979**, *101*, 7001, c) Maruoka, K , Itoh, T , Shirasaka, T , Yamamoto, H *J Am Chem Soc* **1988**, *110*, 310

13 2-Methyl-2-cyclohexenone was prepared from 2-methylcyclohexanone by a halogenation dehydrohalogenation procedure according to Warnhoff, E W , Martin, D G , Johnson, W S *Org Synt* **1963**, Coll Vol 4, 162

14 The thermal Diels-Alder reaction of diene **1** with maleic anhydride in dichloromethane at room temperature without catalyst yielded *endo* selectively (24% isolated yield) a 2 1 mixture of conformers (extended boat and folded boat , respectively) as was determined by correlation of ^{1}H-NMR data with literature data see ref 12b and Overman, L E , Freerks, R L , Petty, C B , Clizbe, L A , Ono, R K , Taylor, G F , Jessup, P J *J Am Chem Soc* **1981**, *103*, 2816

15 The absolute configuration of the racemic adducts is arbitrarily chosen

16 Fringuelli, F , Minuti, L , Radics, L , Taticchi, A , Wenkert, E *J Org Chem* **1988**, *53*, 4607

17 The $AlCl_3$ catalyzed reaction of *R*(-)-carvone with simple dienes gives more than 90% *anti* addition, see ref 7b

18 a) Hydrolysis of the silyl enol ethers to the corresponding ketones is much faster (15 min) with 1N HCl/THF than with 4N HCl in toluene (ref 8c 2 days) probably due to better solvation of the reagents, b) see also Danishefsky, S , Kitahara, T , Yan, C F , Morris, J *J Am Chem Soc* **1979**, *101*, 6996

19 When the stronger Lewis acid $EtAlCl_2$ (50 mol%) was used instead of $ZnCl_2$ the reaction mixture turned black probably due to polymerisation of the diene After workup the *exo* adduct **14b** (< 10%) and an unidentified byproduct was isolated

20 It should be noted that 3-methyl-2-cyclohexenone and 4,4-dimethyl-2-cyclohexenone gave no reaction at all with the pentadienes **1**, **2** and **3** in the presence of a Lewis acid catalyst (50 mol% $EtAlCl_2$) under high pressure (15 kbar) and elevated temperature (50 °C)

21 Aben, R W M , Scheeren, J W *J Org Chem* **1987**, *52*, 365

22 Fringuelli, F , Pizzo, F , Minuti, L , Taticchi, A , Wenkert, E *J Org Chem* **1983**, *48*, 2802

23 a) Piers, E , Hall, T -W *Can J Chem* **1980**, *58*, 2613, b) Angell, E C , Fringuelli, F , Pizzo, F , Minuti, L , Taticchi, A , Wenkert, E *J Org Chem* **1989**, *54*, 1217

24 a) For atractylon see Minato, H , Nagasaki, T *Chem Commun* **1965**, 377, b) For isoalantolactone see Minato, H , Horibe, I *Chem Commun* **1965**, 531, c) For a β-eudesmol precursor see Miller, R B , Nash, R D *J Org Chem* **1973**, *38*, 4424, d) For atractylon and alantolactone see Posner, G H , Loomis, G L *J Org Chem* **1973**, *38*, 4459, e) For arctiol and eudesma-4(14),7(11)-dien-8-one see Torii, S , Inokuchi, T *Bull Chem Soc Jpn* **1980**, *53*, 2642

25 Dolby, L J , Marshall, K S *Org Prep Proced* **1969**, *1*, 229, *Synthesis*, **1971**, 330

26 Calogeropoulou, T , Wiemer, D F *J Org Chem* **1988**, *53*, 2295

27 Jung, M E , McCombs, C A *Org Syn* **1978**, *58*, 163

28 Vedejs, E , Eberlein, T H , Mazur, D J , McClure, C K , Perry, D A , Ruggeri, R , Schwartz, E , Stults, J S , Varie, D L , Wilde, R G , Wittenberger, S *J Org Chem* **1985**, *51*, 1556

29 Corey, E J , Venkateswarlu, A *J Am Chem Soc* **1972**, *94*, 6190

30 J -P G Seerden, H W Scheeren *Tetrahedron Lett* **1993**, *34*, 2669-2672

31 Lanthanide-Induced-Shift (LIS) NMR experiment with *ca* 0 25 equiv (+)-Eu(hfc)$_3$ the singlet signal of the angular methyl group shifted *ca* 1 ppm downfield to give two singlets with equal integration of the two enantiomers

32 Greenwald, R , Chaykovsky, M , Corey, E J *J Org Chem* **1963**, *28*, 1128, Marshall, J A , Pike, M T , Carroll, R D *J Org Chem* **1966**, *31*, 2933, Soffer, M D , Burk, L A *Tetrahedron Lett* **1970**, 211, Huffman, J W , Mole, M L *Tetrahedron Lett* **1971**, 501

33 Nazarov, I N , Bergelson, L D *Zhur Obechei Khim* **1950**, *20*, 648-660

34 Danishefsky, S , Kitahara, T *J Org Chem* **1975**, *40*, 538-539

35 Bauduin, G , Pietrasanta, Y *Tetrahedron Lett* **1973**, *29*, 4225

36 Hajos, Z G , Parrish, D R *J Org Chem* **1974**, *39*, 1615

37 Frank, R L , Hall, Jr , H K *J Am Chem Soc* **1950**, *72*, 1645-1648, Halsall, T G , Thomas, D B *J Chem Soc* **1956**, 2431-2443, Clark, R D , Heathcock, C.H *Synthesis* **1974**, 47-48

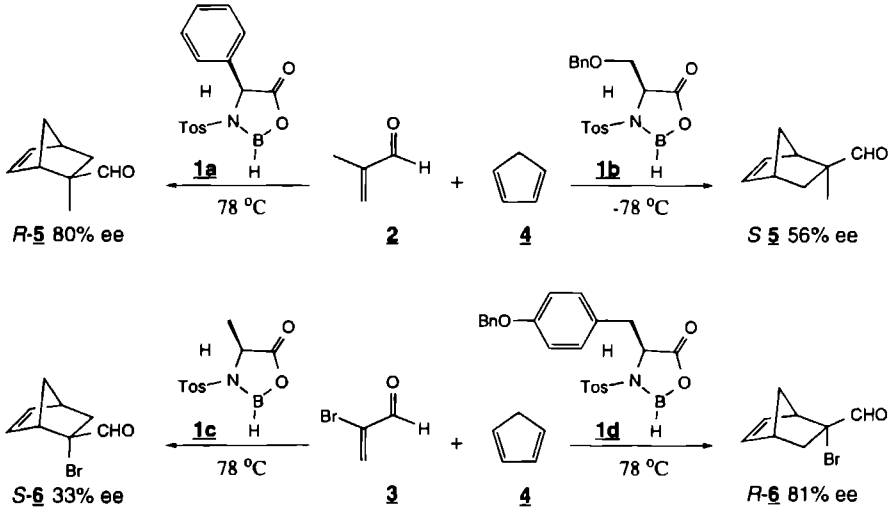
38 Danishefsky, S , Harayama, T , Singh, R K *J Am Chem Soc* **1979**, *101*, 7011

39 For example, a 3-nitro-2-cyclohexenone will give reversed regioselectivity see Corey, E J , Estreicher, H *Tetrahedron Lett* **1981**, *22*, 603-606, Ono, N , Miyake, H , Kamimura, A , Kaji, A *J Chem Soc Perkin Trans I*, **1987**, 1929-1935

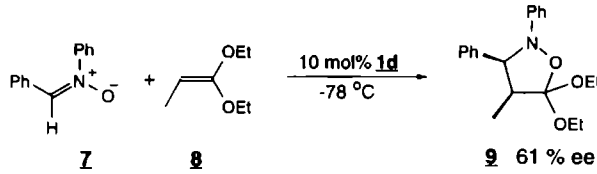
Summary

This thesis describes the design, synthesis and application of some chiral 1,3,2-oxazaborolidines as Lewis acid catalysts for asymmetric cycloaddition reactions In the introductory Chapter 1 a literature survey on the development and use of chiral Lewis acids in asymmetric catalysis is given

In chapter 2 chiral 1,3,2-oxazaborolidines **1a**-**d**, derived simply from sulfonamides of α-amino acids and borane, have been used as chiral Lewis acid catalysts for the asymmetric Diels-Alder reaction of α,β–enals, e g methacrolein **2** and 2-bromoacrolein **3**, with cyclopentadiene **4** The enantioselectivity of this quantitative and *exo*-selective reaction is controlled by the presence, or absence, of donor atoms at the appropriate position in the α-side-chain substituent of the chiral ligand Attractive donor-acceptor interactions between ligand and substrate can lead to a reversal of enantioselectivity (as for **1b** and **1d**), compared with repulsive non-bonded interactions with sterically demanding side-chain substituents (as for **1a** and **1c**) Thus, both enantiomers of the cycloadducts **5** and **6** have been prepared starting from *L*-amino acids as chiral ligands

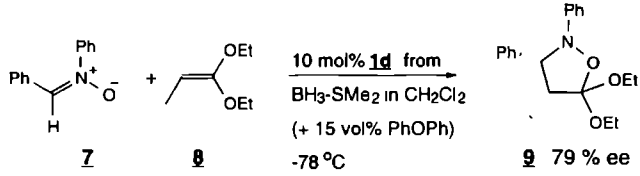


Chapter 3 describes the first examples of asymmetric 1,3-dipolar cycloadditions of various (a)cyclic nitrones, e g **7**, with electron-rich ketene O,O-dialkylacetals catalyzed by chiral oxazaborolidines The reaction of nitrones with 1,1-dialkoxypropenes, e g **8**, proceeds regio- and stereoselectively to give the *cis*-5,5-dialkoxy-4-methyl-isoxazolidines, e g **9**, in high yield It is proposed that the Lewis acid complexes to the nitrone-oxygen atom thereby lowering the LUMO energy of the nitrone This facilitates the reaction with electron-rich alkenes, such as ketene acetals Generally, chiral oxazaborolidine **1d**, derived from *L*-tyrosine(O-benzyl ether), gave the best enantioselectivities Attractive donor-acceptor interactions between side-chain substituent of the ligand and the nitrone are assumed to control these enantioselectivities



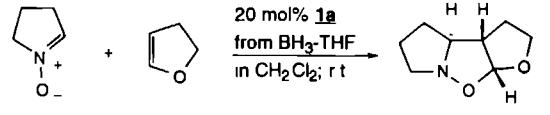
7 8 9 61 % ee

Chapter 4 descibes the dramatic influence of the solvent on the enantioselectivity of the 1,3-dipolar cycloaddition of nitrones with ketene acetals catalyzed by chiral oxazaborolidines. It was found that the addition of a co-solvent with shape and properties similar to the side-chain substituent can lead to a reversal of enantioselectivity. Thus, both enantiomers of the cycloadducts, e.g. **9**, have been prepared from a single chiral source by choosing the appropriate solvent composition.



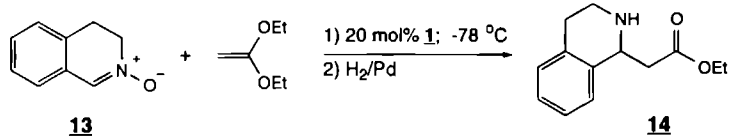
7 8 9 79 % ee

Chapter 5 describes the application of chiral oxazaborolidine catalysts to the asymmetric 1,3-dipolar cycloaddition of nitrones to alkyl enol ethers. The regioselective reaction of ethyl vinyl ether with various nitrones is catalyzed by chiral oxazaborolidines. Unfortunately, the 5-ethoxyisoxazolidines are obtained as mixtures of *endo*- and *exo*-isomers, and without enantioselectivity On the contrary, the catalyzed reaction of pyrroline N-oxide **10** with excess 2,3-dihydrofuran **11** gives the tricylic *exo*-cycloadduct **12**. So far, the highest enantioselectivity has been obtained with the chiral oxazaborolidine **1a**.



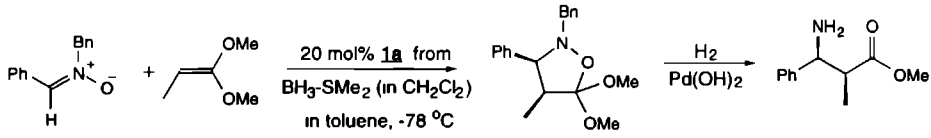
10 11 *exo*-12 38% ee

Chapter 6 describes a two-step catalytic asymmetric synthesis of chiral β-amino esters. Chiral oxazaborolidine catalyzed 1,3-dipolar cycloaddition reactions of nitrones, e.g. **13**, with ketene acetals affords 5,5-dialkoxyisoxazolidines which can serve as versatile intermediates for the synthesis of valuable chiral β-amino esters, e.g. **14**, by mild hydrogenolysis of the N-O bond.



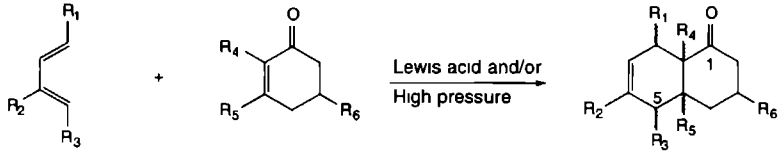
13 14

The use of N-benzyl nitrones, e g **15**, in this strategy is particularly interesting since hydrogenolysis of *cis*-5,5-dialkoxyisoxazolidines gives, in one step, the corresponding *syn*-β-amino esters, e g **16**, with a free amino group



15 **16** 74 % ee

Chapter 7 describes the (chiral) Lewis acid and/or high-pressure-promoted Diels-Alder reactions of functionalized dienes **17** with 2-cyclohexenones **18** The Lewis acid catalyzed Diels-Alder reactions of cyclohexenones with electron-rich 1,3-pentadienes proceed regioselectively The regioselectivity is controlled by donor-substituents R_1 and/or R_2 at C-1 or C-3, respectively In general, mixtures of *endo*- and *exo*-cycloadducts **19** are obtained in moderate yields The use of high pressure has no effect on the regio- or stereoselectivity

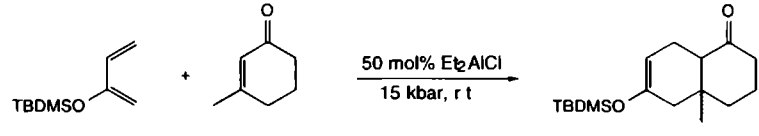


17 R_1 = H, OMe; R_2 = H, OTMS, OTBDMS; R_3 = H, Me

18 R_4 = H, Me; R_5 = H, Me; R_6 = H (Me)C=CH_2

19

The Lewis acid/high-pressure-promoted Diels-Alder reaction of 2-*tert*-butyldimethylsilyloxy-1,3-butadiene with 3-methyl-2-cyclohexenone affords a mixture of *endo*- and *exo*-cycloadducts **20** which can be converted into a versatile synthon for eudesmane-type sesquiterpenes Unfortunately, chiral oxazaborolidines were not strong enough to promote the Diels-Alder reactions of 2-cyclohexenones with electron-rich dienes

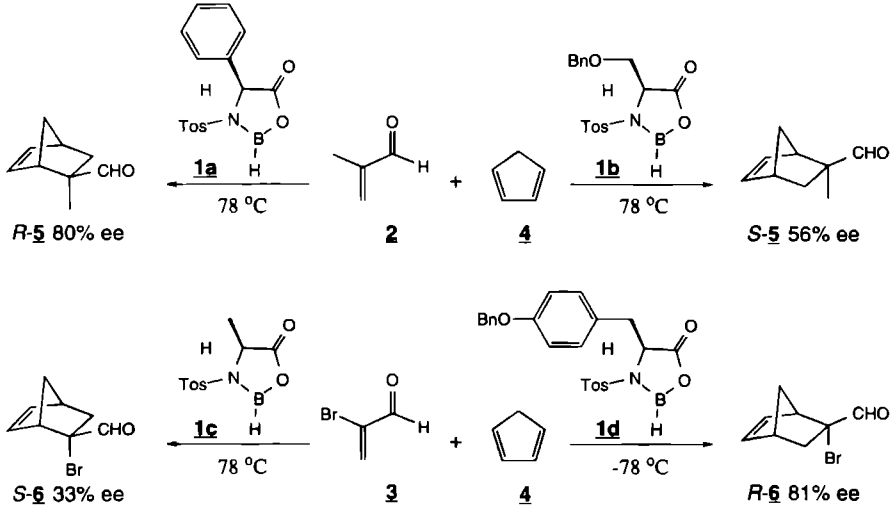


20

Samenvatting

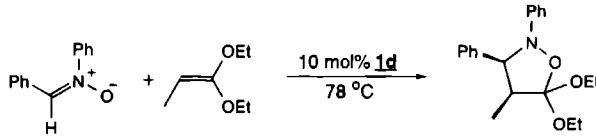
Dit proefschrift beschrijft het ontwerpen, synthetiseren en toepassen van chirale 1,3,2-oxazaborolidines als lewiszure katalysatoren voor asymmetrische cycloadditiereacties In het inleidende Hoofdstuk 1 wordt een literatuuroverzicht gegeven van de ontwikkeling en het gebruik van chirale lewiszuren in de asymmetrische katalyse

In hoofdstuk 2 worden chirale 1,3,2-oxazaborolidines **1**, welke eenvoudig te bereiden zijn uit sulfonamides van α-aminozuren en boraan, gebruikt als chirale lewiszure katalysatoren voor de asymmetrische diels-alderreactie van α,β–onverzadigde aldehydes, zoals methacroleine **2** en 2-broomacroleine **3**, met cyclopentadieen **4** De enantioselectiviteit van deze kwantitatief en *exo*-selectief verlopende reactie wordt bepaald door de aan- of afwezigheid van donor-atomen op de juiste positie in de α-zijketensubstituent van het chirale ligand Aantrekkende donor-acceptorinteracties tussen ligand en substraat kunnen leiden tot een omkering van de enantioselectiviteit (zoals gevonden voor **1b** en **1d**), dit in tegenstelling tot afstotende interacties in het geval van sterische zijketensubstituenten (zoals bij **1a** en **1c**), die niet tot een dergelijke omkering aanleiding geven Door een juiste keuze van de chirale liganden kunnen beide enantiomeren van de cycloadducten **5** en **6** apart worden gemaakt



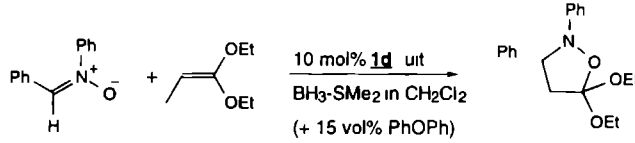
In hoofdstuk 3 worden de eerste voorbeelden gepresenteerd van asymmetrische 1,3-dipolaire cycloaddities van diverse (a)cyclische nitronen, zoals **7**, met elektronen-rijke keteen O,O-dialkylacetalen gekatalyseerd door chirale oxazaborolidines De reactie van nitronen met 1,1-dialkoxypropenen, zoals **8**, verloopt regio- en stereoselectief onder vorming van *cis*-5,5-dialkoxy-4-methyl-isoxazolidines, zoals **9**, die in hoge opbrengst worden verkregen Voorgesteld wordt dat het lewiszuur complexeert met het zuurstofatoom van het nitron waardoor de LUMO energie van de laatste verbinding afneemt Dit vergemakkelijkt de reactie met elektronen-rijke alkenen, zoals

keteenacetalen In het algemeen worden de hoogste enantioselectiviteiten verkregen met het chirale oxazaborolidine **1d**, welke is afgeleid van *L*-tyrosine(O-benzylether) Aantrekkende donor-acceptorinteracties tussen de zijketensubstituent van het ligand en het nitron bepalen waarschijnlijk de enantioselectiveit



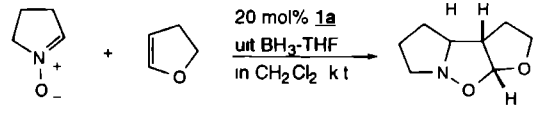
7 **8** **9** 61 % ee

In hoofdstuk 4 wordt de dramatische invloed van het oplosmiddel beschreven op de enantioselectiviteit van de 1,3-dipolaire cycloadditie van nitronen met keteenacetalen gekatalyseerd door chirale oxazaborolidines De aanwezigheid van een co-solvent met vorm en eigenschappen vergelijkbaar met die van de zijketensubstituent blijkt een omkering van de enantioselectiviteit tot stand te brengen Uitgaande van één chirale bron kunnen nu beide enantiomeren van de cycloadducten, zoals **9**, worden gesynthetiseerd door een geschikte combinatie van oplosmiddelen te kiezen



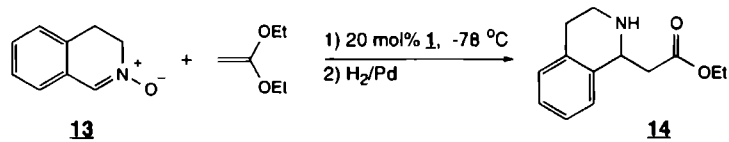
7 **8** **9** 79 % ee

Hoofdstuk 5 beschrijft de toepassing van chirale oxazaborolidine-katalysatoren in de asymmetrische 1,3-dipolaire cycloadditie van nitronen met alkylenolethers De regioselectieve reactie van ethylvinylether met diverse nitronen wordt gekatalyseerd door chirale oxazaborolidines Helaas worden de 5-ethoxyisoxazolidine-producten zonder enige enantioselectiviteit verkregen als een mengsel van *endo*- en *exo*-isomeren De chirale oxazaborolidine gekatalyseerde reactie van pyrroline N-oxide **10** met een overmaat 2,3-dihydrofuran **11** geeft echter *exo* selectief het tricyclische cycloadduct **12** Tot op heden werd de hoogste enantioselectiviteit bereikt met chiraal oxazaborolidine **1a**



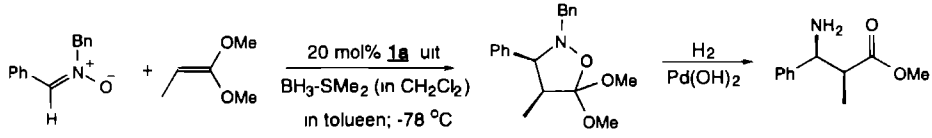
10 **11** *exo*-**12** 38% ee

In hoofdstuk 6 wordt een twee-staps katalytische asymmetrische synthese van chirale β aminoesters beschreven De door chirale oxazaborolidine gekatalyseerde 1,3-dipolaire cycloadditie van nitronen, zoals **13**, met keteenacetalen geven 5,5-dialkoxyisoxazolidines Deze producten kunnen na afloop van de cycloadditie dienen als bruikbare intermediairen voor de synthese van waardevolle chirale β-aminoesters, zoals **14**, wanneer milde hydrogenolyse van de N-O binding wordt toegepast



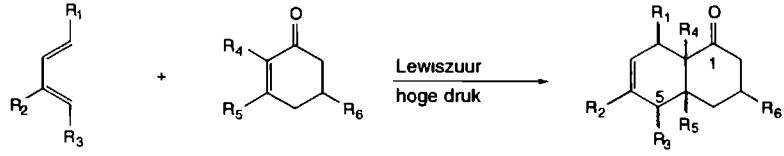
13 14

Het gebruik van N-benzylnitronen, zoals **15**, is in deze strategie bijzonder aantrekkelijk, omdat hydrogenolyse van de *cis*-5,5-dialkoxyisoxazolidines in één stap de overeenkomstige *syn*-β-aminoesters oplevert, bijvoorbeeld **16**, die een vrije aminogroep bezitten.



15 16 74 % ee

Hoofdstuk 7 beschrijft de door (chirale) lewiszuren- en hoge druk-gekatalyseerde diels-alderreacties van gefunctionaliseerde diënen **17** met 2-cyclohexenonen **18**. De lewiszuur-gekatalyseerde diels-alderreacties van 2-cyclohexenonen met elektronen-rijke 1,3-pentadiënen verlopen regioselectief. De regioselectiviteit wordt gestuurd door de donor-substituenten R_1 en R_2 op C-1 en C-3 van het dieen. In het algemeen worden mengsels van *endo*- en *exo*-cycloadducten **19** in matige opbrengst verkregen. Het gebruik van hoge druk heeft geen effect op de regio- of stereoselectiviteit van de reacties.

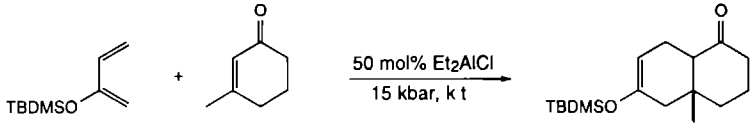


17 R_1 = H, OMe; R_2 = H, OTMS, OTBDMS; R_3 = H, Me

18 R_4 = H, Me; R_5 = H, Me; R_6 = H, (Me)C=CH_2

19

De door lewiszuren en hoge druk gekatalyseerde diels-alderreactie van 2-*tert*-butyldimethylsilyloxy-1,3-butadieen met 3-methyl-2-cyclohexenon geeft een mengsel van *endo*- en *exo*-cycloadducten **20** die samen omgezet kunnen worden in een bruikbaar synthon voor eudesmaan-type sesquiterpenen. Helaas bleken de chirale oxazaborolidines niet sterk genoeg te zijn om de diels-alderreacties van 2-cyclohexenonen met elektronenrijke diënen te katalyseren.



20

Epiloog

Het onderzoek, dat beschreven is in dit proefschrift, werd uitgevoerd in het kader van het Innovatiegerichte onderzoeksprogramma (IOP) Katalyse van het Ministerie van Economische Zaken Het IOP-Katalyse beoogt een samenwerking te bewerkstelligen tussen universiteit en industrie die uiteindelijk nieuwe economische activiteit in Nederland moet opleveren Het doel van het onderzoek was het ontwerpen, bereiden en testen van selectieve lewiszure katalysatoren in zogenaamde asymmetrische diels-alderreacties en verwante cycloadditiereacties De verworven kennis moet in principe kunnen dienen als basis voor een nieuwe en schonere technologie voor de farmaceutische, agrochemische en de geur- en smaakstoffenindustrie

Het is bekend dat enantiomere verbindingen - dit zijn verbindingen die elkaars spiegelbeeld zijn - zoals sommige medicijnen en geur- en smaakstoffen een verschillende biologische activiteit kunnen vertonen Om nieuwe producten op de markt te kunnen brengen is, mede onder druk van een nieuwe wetgeving op dit gebied, de selectieve bereiding van enantiomeerzuivere verbindingen van essentieel belang Tot op heden werd hiervoor voornamelijk de klassieke kinetische resolutie van enantiomeren op grote schaal toegepast, waarbij echter 50% van het product verloren gaat Dit proces geeft bovendien grote afvalstromen Het meest veelbelovende alternatief voor de bereiding van enantiomeerzuivere verbindingen is het gebruik van optisch actieve katalysatoren Over het algemeen verlopen gekatalyseerde reacties veel sneller, selectiever en schoner dan niet-gekatalyseerde reacties Met optisch zuivere katalysatoren kunnen de reacties bovendien asymmetrisch verlopen, waarbij één van beide enantiomere producten in overmaat wordt verkregen

In het onderzoek dat in dit proefschrift wordt beschreven werden optisch actieve oxazaborolidines ontworpen, bereid en getest als chirale lewiszure katalysatoren voor asymmetrische cycloadditiereacties De resultaten van dit onderzoek laten zien dat oxazaborolidines voortreffelijke eigenschappen bezitten, die als volgt zijn te omschrijven

1) ze zijn eenvoudig uit goedkope grondstoffen (α-aminozuren) te bereiden,
2) ze laten een grote variatie toe aan substituenten, waardoor de reactiviteit van de katalysator en de selectiviteit van de reactie gestuurd kan worden,
3) ze zijn breed toepasbaar bij asymmetrische reacties, zoals de synthetisch belangrijke diels-alderreactie en 1,3-dipolaire cycloadditiereacties ,
4) ze maken het mogelijk dat enantiomere producten kunnen worden bereid uitgaande van één en dezelfde katalysator door de reactieomstandigheden te variëren,
5) de voor de katalysatorbereiding benodigde α-aminozuren kunnen volledig worden teruggewonnen en efficient worden hergebruikt,
6) ze bieden de mogelijkheid tot verankering aan vaste dragers, waardoor ze als heterogene katalysatoren kunnen worden worden toegepast

Uit het bovenstaande kan geconcludeerd worden dat oxazaborolidines geschikte katalysatoren zijn voor mogelijke industriele toepassingen Hierbij wordt vooral gedacht aan de bereiding van steroiden, alkaloiden en terpenen

Publications and Presentations

1 *Unexpectedly High Diastereomeric Induction in the Diels-Alder Reaction of Quinones with Chiral Aryl-containing 1-Alkoxy 3-trimethylsilyloxy-buta-1,3-dienes*", J F M de Bie, G P F van Strijdonck, J -P G Seerden, G Beurskens, J W Scheeren, *Tetrahedron Lett* **1990**, *31*, 7233-7236

2 "*Sterecontrolled Synthesis of 3-(Ethoxycarbonyl)-4-hydroxy-2-isoxazoline 2-Oxides A New Approach to the Synthesis of 4-Hydroxylated 2-Isoxazolines*", G Rosini, E Marotta, P Righi, J -P G Seerden, *J Org Chem* **1991**, *56*, 6258-6260

3 "*Asymmetric Diels-Alder Reactions Catalyzed by Chiral Oxazaborolidines Effect of the Position of an Electron-donor Functionality in the α-Side Chain Substituent on the Enantioselectivity*", J -P G Seerden, J W Scheeren, *Tetrahedron Lett* , **1993**, *34*, 2669-2672

4 "*Asymmetric 1,3-Dipolar Cycloaddition of Nitrones with Ketene Acetals Catalyzed by Chiral Oxazaborolidines*", J -P G Seerden, A W A Scholte op Reimer, J W Scheeren, *Tetrahedron Lett* **1994**, *35*, 4419-4422

5 "*Dramatic Solvent Effects on the Enantioselectivity of Chiral Oxazaborolidine Catalyzed Asymmetric 1,3-Dipolar Cycloadditions of Nitrones with Ketene Acetals* ', J -P G Seerden, M M M Kuypers, J W Scheeren, *Tetrahedron Asymmetry* **1995**, *6*, 1441 1450

6 "*Asymmetric 1,3-Dipolar Cycloaddition of Nitrones with Ketene Acetals Catalyzed by Chiral Oxazaborolidines*", J -P G Seerden, A W A Scholte op Reimer, M M M Kuypers, J W Scheeren, oral presentation (OP-33) on the 6th International Kyoto Conference on Organic Chemistry (IKCOC-6), Kyoto, Japan, 7-11 november 1994

7 "*Chiral Oxazaborolidine Catalyzed Asymmetric Cycloaddition Reactions*", J -P G Seerden, lecture at Nagoya University, Nagoya, Japan, 10 november 1994

8 "*Chiral Oxazaborolidine Catalyzed Asymmetric 1,3-Dipolar Cycloaddition of Nitrones with Enol Ethers*", J -P G Seerden, M M M Boeren, J W Scheeren, *in preparation*

Curriculum Vitae

De schrijver van dit proefschrift werd geboren op 21 augustus 1966 te Weert In juni 1984 werd het V W O -diploma behaald aan de Philips van Horne Scholengemeenschap te Weert In hetzelfde jaar werd begonnen met de studie scheikunde aan de Katholieke Universiteit Nijmegen (KUN) Het doctoraal examen werd in augustus 1990 behaald met als hoofdvak Organische Chemie (Dr J W Scheeren) en als uitgebreide nevenrichting Biochemie (Prof Dr J J H H M de Pont) In het kader van het ERASMUS-programma werd een extra stage Organische Chemie vervuld aan de Universiteit van Bologna, Italie (Prof Dr G Rosini) Van oktober 1990 tot en met december 1990 was hij werkzaam als junior onderzoeker aan de KUN bij de vakgroep Organische Chemie (Dr J W Scheeren), binnen het taxol-project (sponsor Pharmachemie B V) Van januari 1991 tot en met december 1994 werd in hetzelfde laboratorium in het kader van het IOP Katalyse het in dit proefschrift beschreven promotie onderzoek uitgevoerd als assistent-in-opleiding (AIO) onder leiding van Dr J W Scheeren en Prof Dr R J M Nolte Van 1 april tot en met 1 augustus 1995 was hij in dezelfde groep werkzaam als onderzoeker aan een project omtrent chirale katalysatoren aan een vaste drager Vanaf 1 augustus 1995 werkt hij als post-doc in de vakgroep Organische Chemie (KUN) aan een project gefinancierd door Solvay Duphar B V